Unit 3.3 Mechanisms of Information Transfer & Regulation

AP Biology

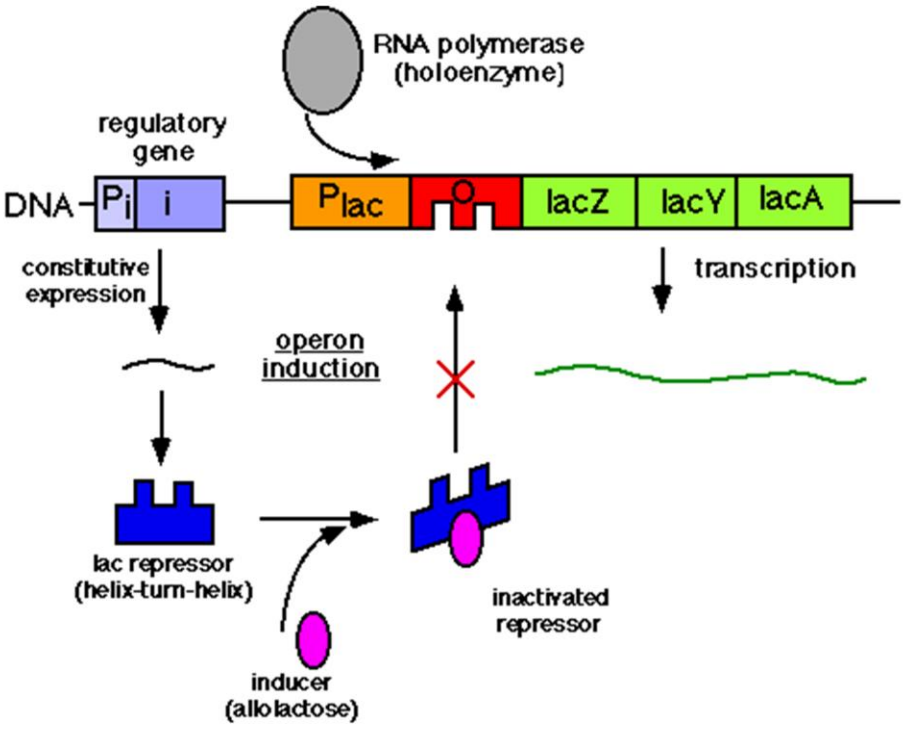
Mrs. Petrov

Part 1: Gene Regulation Strategies

Bacteria

- Natural selection has favored bacteria that produce only the products **needed** by that cell
- A cell can regulate the production of enzymes by **feedback inhibition** or by **gene regulation**
- Gene expression in bacteria is controlled by the **operon** model

Operons: The Basic Concept



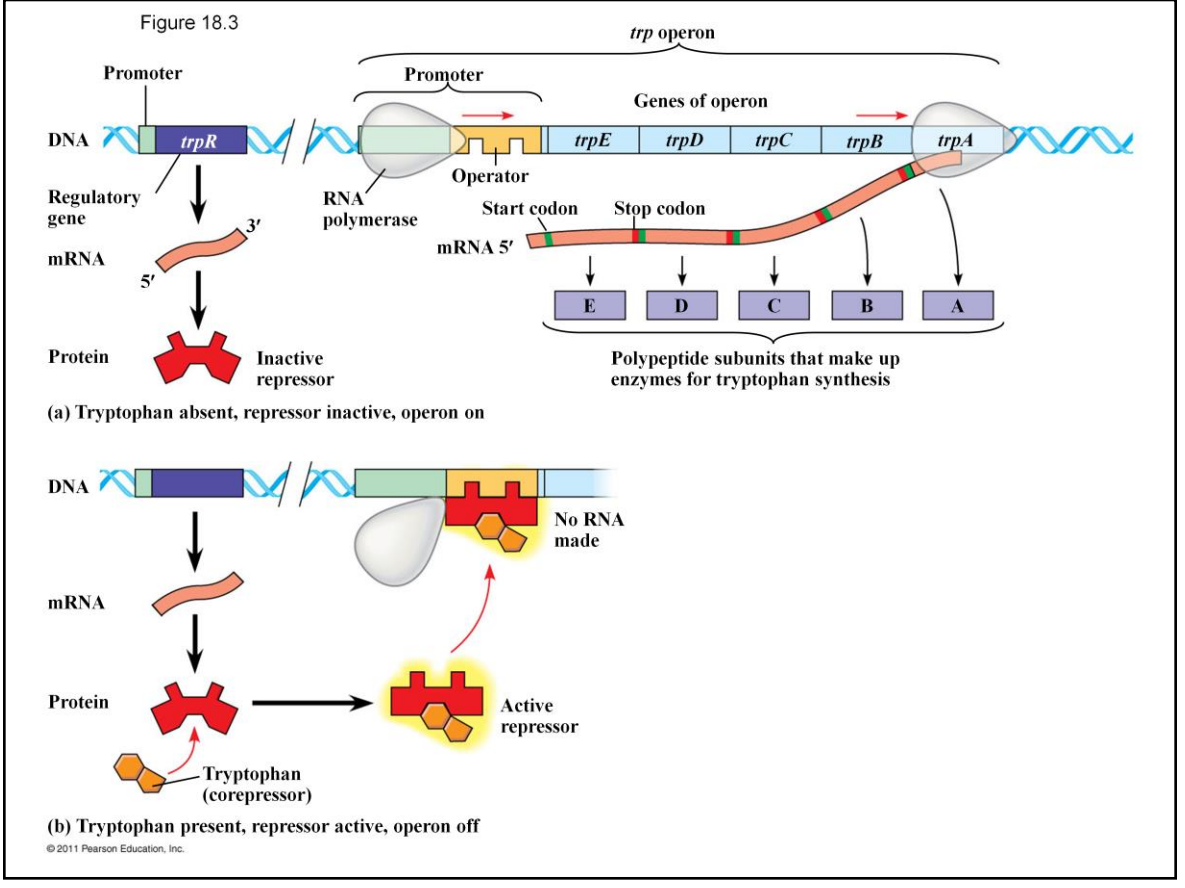
A cluster of functionally related genes can be controled by a single "on-off switch" called an operator.

An **operon** is the entire stretch of DNA that includes the operator, the promoter, and the genes that they control

There is usually a regulatory gene that encodes for making a repressor protein that inhibits the gene's own transcription!

The repressor can be in an **active** or **inactive** form, depending on the presence of other molecules

A **corepressor** is a molecule that cooperates with a repressor protein to switch an operon off



For example, *E. coli* can synthesize the amino acid tryptophan

By default the *trp* operon is on and the genes for tryptophan synthesis are transcribed

Use the top diagram to explain why the operon is ON

When tryptophan is present, it binds to the *trp* repressor protein, which turns the operon off

How does this happen?

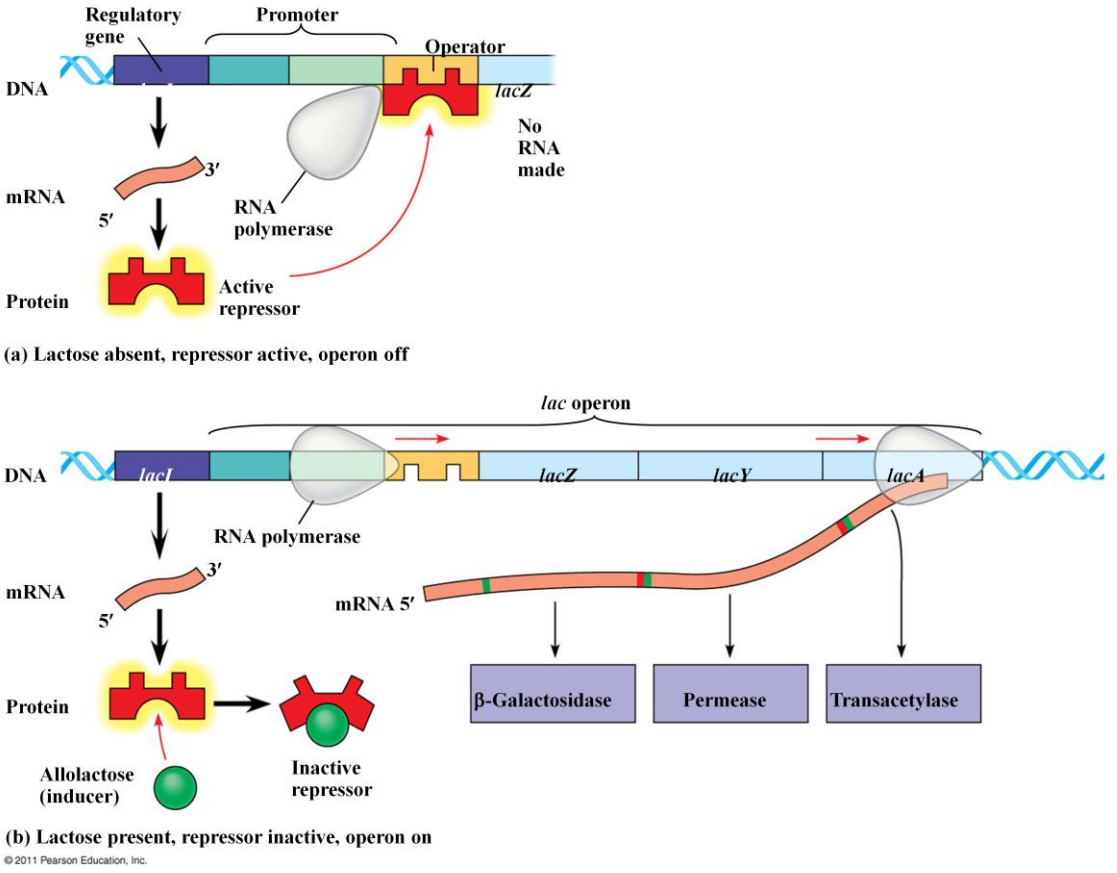
The repressor is active only in the presence of its corepressor tryptophan; thus the *trp* operon is turned off (repressed) if tryptophan levels are high

What type of regulation pathway does this represent?

Repressible and Inducible Operons: Two Types of Negative Gene Regulation

- A **repressible** operon is one that is usually **on**; binding of a repressor to the operator shuts **off** transcription
- The *trp* operon is a repressible operon

- An **inducible** operon is one that is usually **off**; a molecule called an inducer inactivates the repressor and turns **on** transcription



The *lac* operon is an inducible operon and contains genes that code for enzymes used in the metabolism of lactose

By itself, the *lac* repressor is active and switches the *lac* operon off

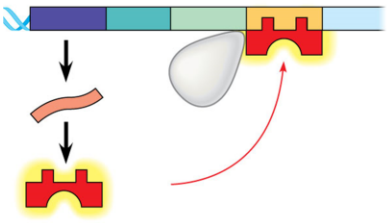
A molecule called an **inducer** inactivates the repressor to turn the *lac* operon on

What is the inducer in this example?

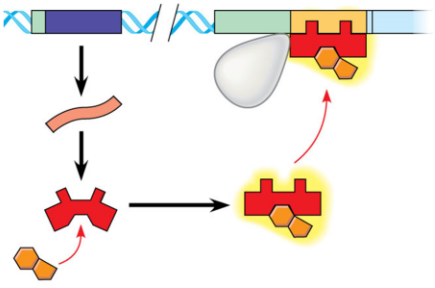
How is this similar to the trp operon? Different?

- Regulation of the *lac* and trp operons involves **NEGATIVE** control of genes because **operons are switched off** by the **active form of the repressor.**

Negative- Inducible



Negative - Repressible



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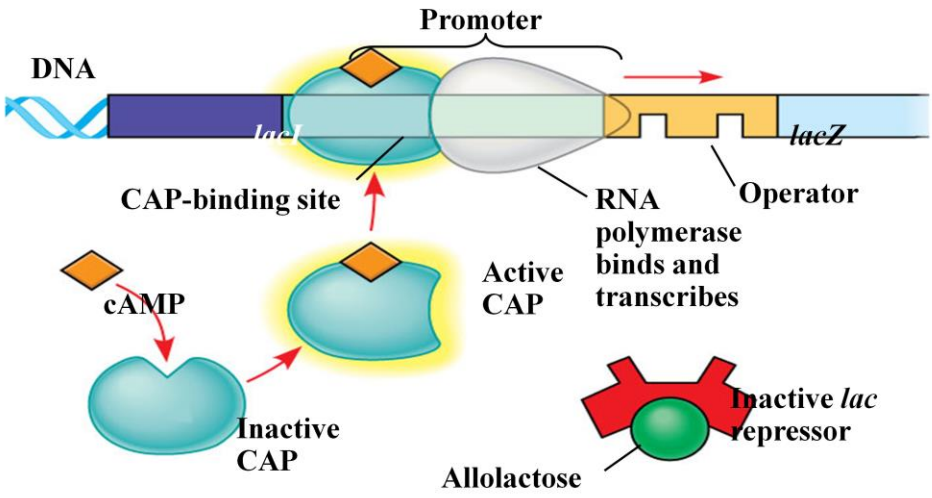
Positive Gene Regulation

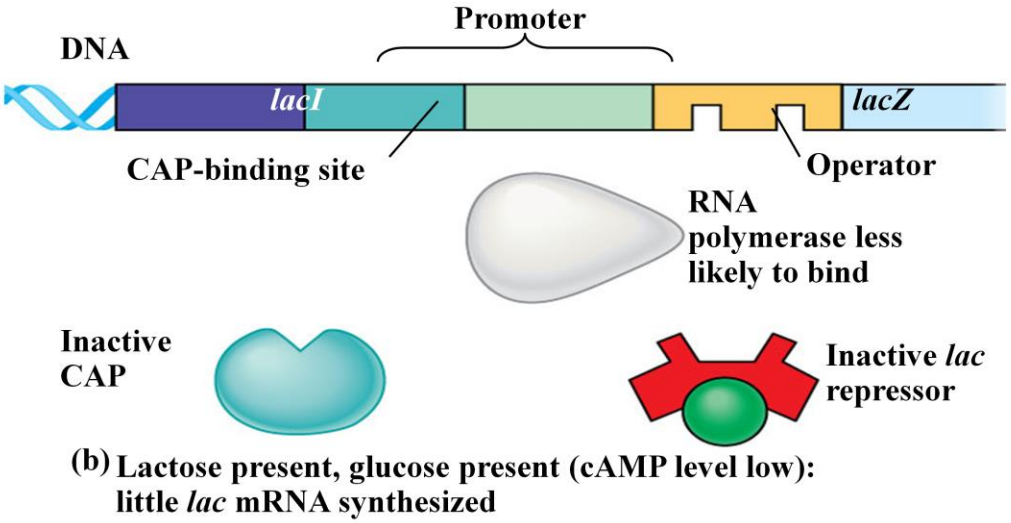
- Some operons are also subject to positive control through a stimulatory protein, such as catabolite activator protein (CAP), an **activator** of transcription



(a) Lactose present, glucose scarce (cAMP level high): abundant *lac* mRNA synthesized

When glucose (preferred by *E. coli*) is scarce, CAP is activated by binding with **cyclic AMP (cAMP)**

Activated CAP attaches to the promoter of the *lac* operon and increases the affinity of RNA polymerase, thus accelerating transcription



(b) Lactose present, glucose present (cAMP level low): little *lac* mRNA synthesized

When glucose levels increase, CAP detaches from the *lac* operon, and transcription returns to a normal rate

1. Which of the following is a protein produced by a regulatory gene?

A) operon

B) inducer

C) promoter

D) repressor

2. A lack of which molecule would result in the cell's inability to "turn off" genes?

A) operon

B) corepressor

C) promoter

D) Inducer

3. A mutation that inactivates the regulatory gene of a repressible operon in an *E. coli* cell would result in

A) continuous transcription of the structural gene controlled by that regulator.

B) complete inhibition of transcription of the structural gene controlled by that regulator.

C) irreversible binding of the repressor to the operator.

D) continuous translation of the mRNA because of alteration of its structure

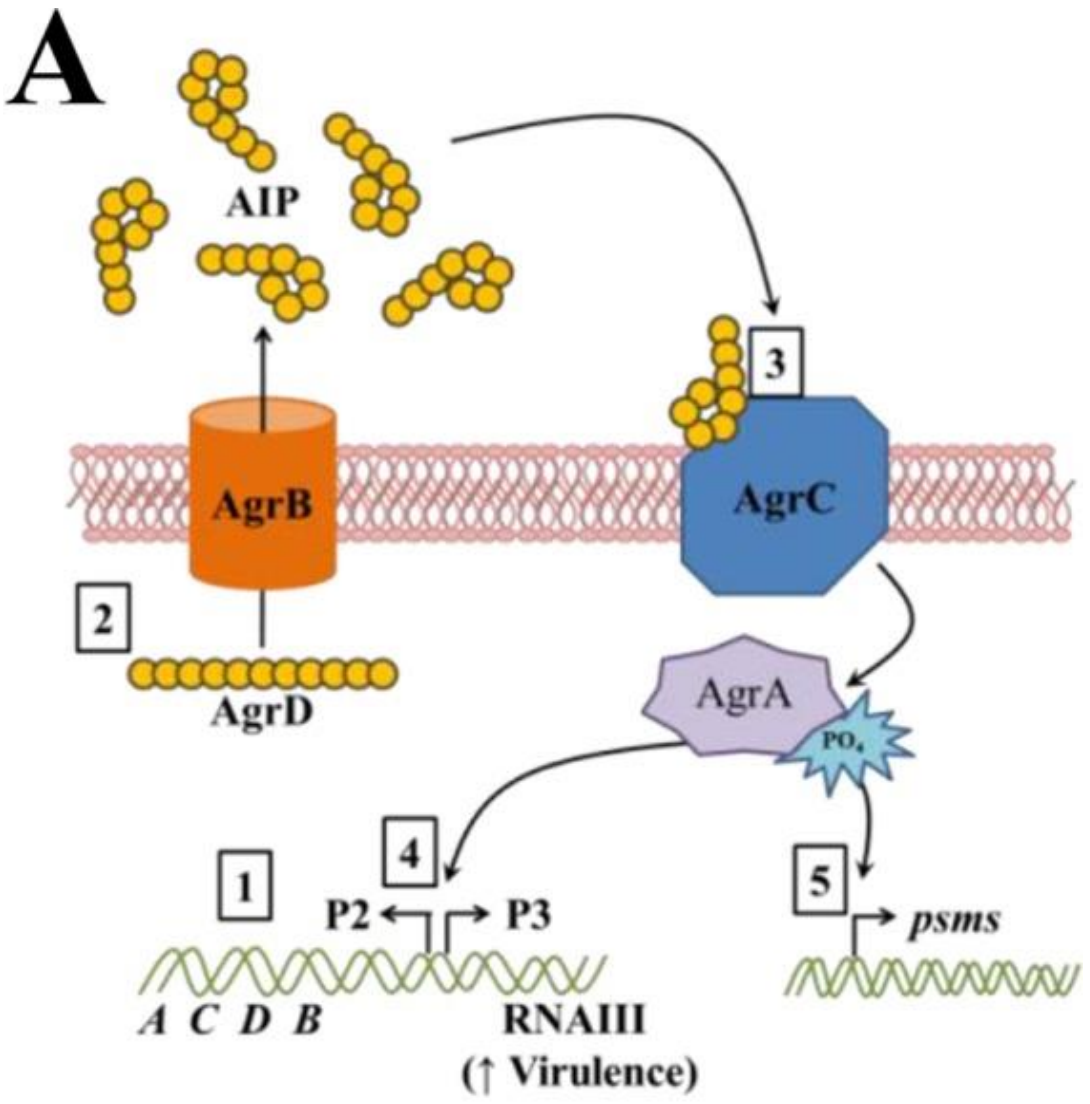
4. For a repressible operon to be transcribed, which of the following must occur?

A) A corepressor must be present.

B) RNA polymerase and the active repressor must be present.

C) RNA polymerase must bind to the promoter, and the repressor must be inactive.

D) RNA polymerase cannot be present, and the repressor must be inactive.



Schematic of the *MRSA* accessory gene regulator quorum-sensing system.

1, The *agr* P2 promoter drives the expression of the four genes of the operon *agrBDCA*.

2, AgrD is a propeptide that is cyclized to form autoinducing peptide (AIP) and secreted via AgrB.

3, Secreted AIP binds to its cognate receptor AgrC, activating it, leading to the phosphorylation of AgrA.

4, AgrA binds to the divergent promoters P2 and P3 as well as the promoters for the transcription of the phenol-soluble modulin (PSM) toxins.

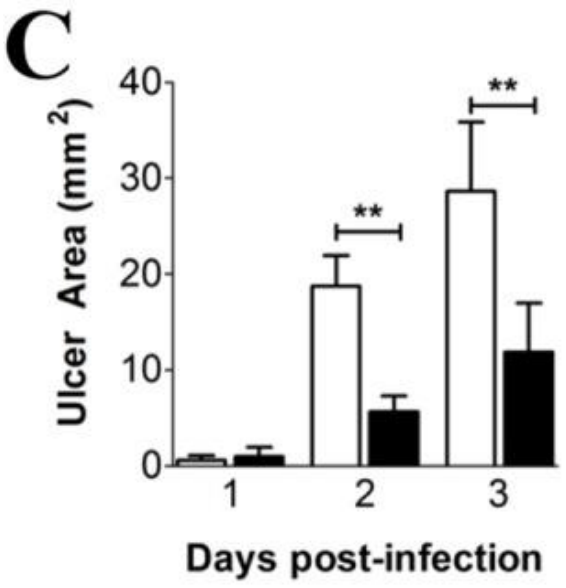
5, P2 drives a positive-feedback loop resulting in the upregulation of the *agr* operon, whereas P3 drives the transcription of the effector molecule RNAIII. RNAIII leads to the upregulation of virulence factors that contribute to invasive infection.

5. Which of the following elements are not part of the operon?
    a. P2
    b. P3
    c. agrB
    d. AgrC

6. Which of the following is not accounted for in the schematic?
    a. Structural Genes
    b. Metabolites
    c. Promoters
    d. Repressors

7. The most accurate description of this system is
    a. The operon is an example of negative control whereby RNAIII is an inducer.
    b. The operon is an example of negative control whereby RNAIII is an activator.
    c. The operon is an example of positive control whereby AgrA is an inducer.
    d. The operon is an example of positive control whereby AgrA is an activator.

8. Altering patterns of gene expression in prokaryotes would most likely serve the organism's survival in which of the following ways?
    a. organizing gene expression so that genes are expressed in a given order
    b. allowing each gene to be expressed an equal number of times
    c. allowing the organism to adjust to changes in environmental conditions
    d. allowing environmental changes to alter the prokaryote's genome



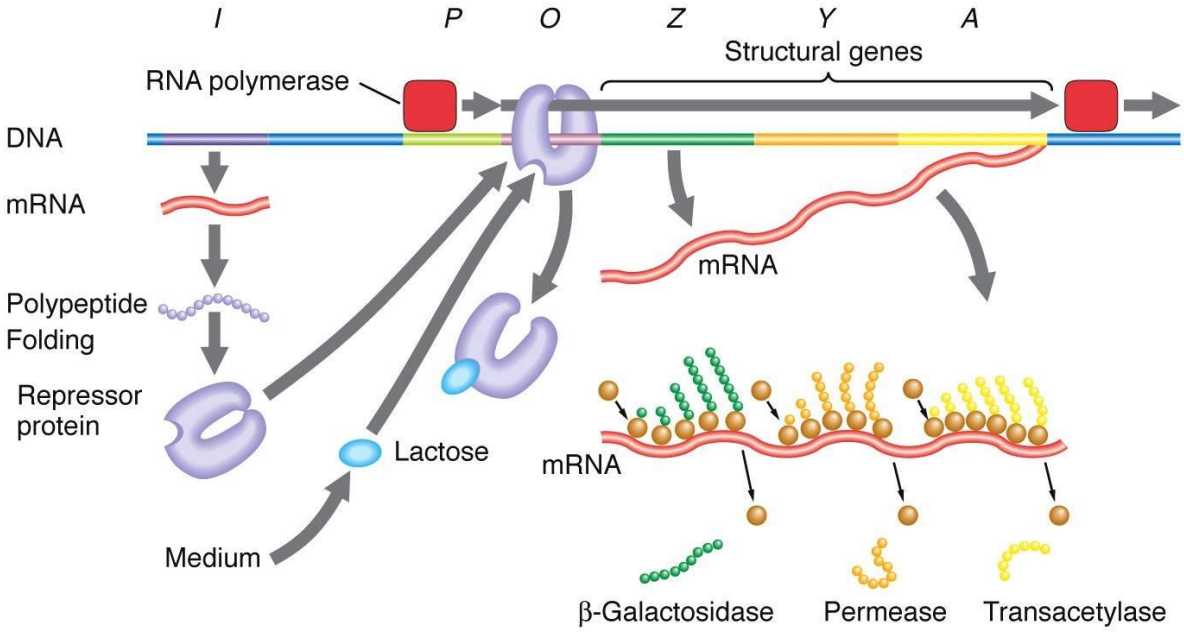
The figure above shows infected cells untreated (white bars) and treated (black bars) with a drug that binds to RNAIII.

1. Which of the following best explains why the treatment did not completely eliminate ulcers caused by the infection?
    a. Mutations occur during transcription of the gene encoding RNAIII.
    b. The RNAIII of other bacteria were unaffected.
    c. The P2 promoter was still functional.
    d. The agrC receptor protein was still functional.

2. Which of the following questions would least likely be considered when deciding if this drug should be used in regards to safety?
    a. Will other virulent bacteria also be affected?
    b. Will other beneficial bacteria also be affected?
    c. Will the human host cells also be affected?
    d. Will the chemical cause any environmental impacts?

3. Calculate how many times more effective the treatment was versus no treatment for the day 3 data.

4. Explain which data set day would be considered most statistically significant.



Suppose an experimenter becomes proficient with a technique that allows her to move DNA sequences within the Lac Operon depicted below:

1. If she moves the promoter for the *lac* operon to the region between the *beta galactosidase* gene and the *permease* gene, which of the following would be likely? Assume lactose is present.

A) Beta galactosidase will be produced.

B) RNA polymerase will no longer transcribe permease.

C) The operon will no longer be inducible.

D) Three structural genes will no longer be expressed.

2. If she moves the repressor gene (*lac* I), along with its promoter, to a position at some several thousand base pairs away from its normal position, which will you expect to occur?

A) The repressor will no longer be made.

B) The repressor will no longer bind to the operator.

C) The *lac* operon will function normally

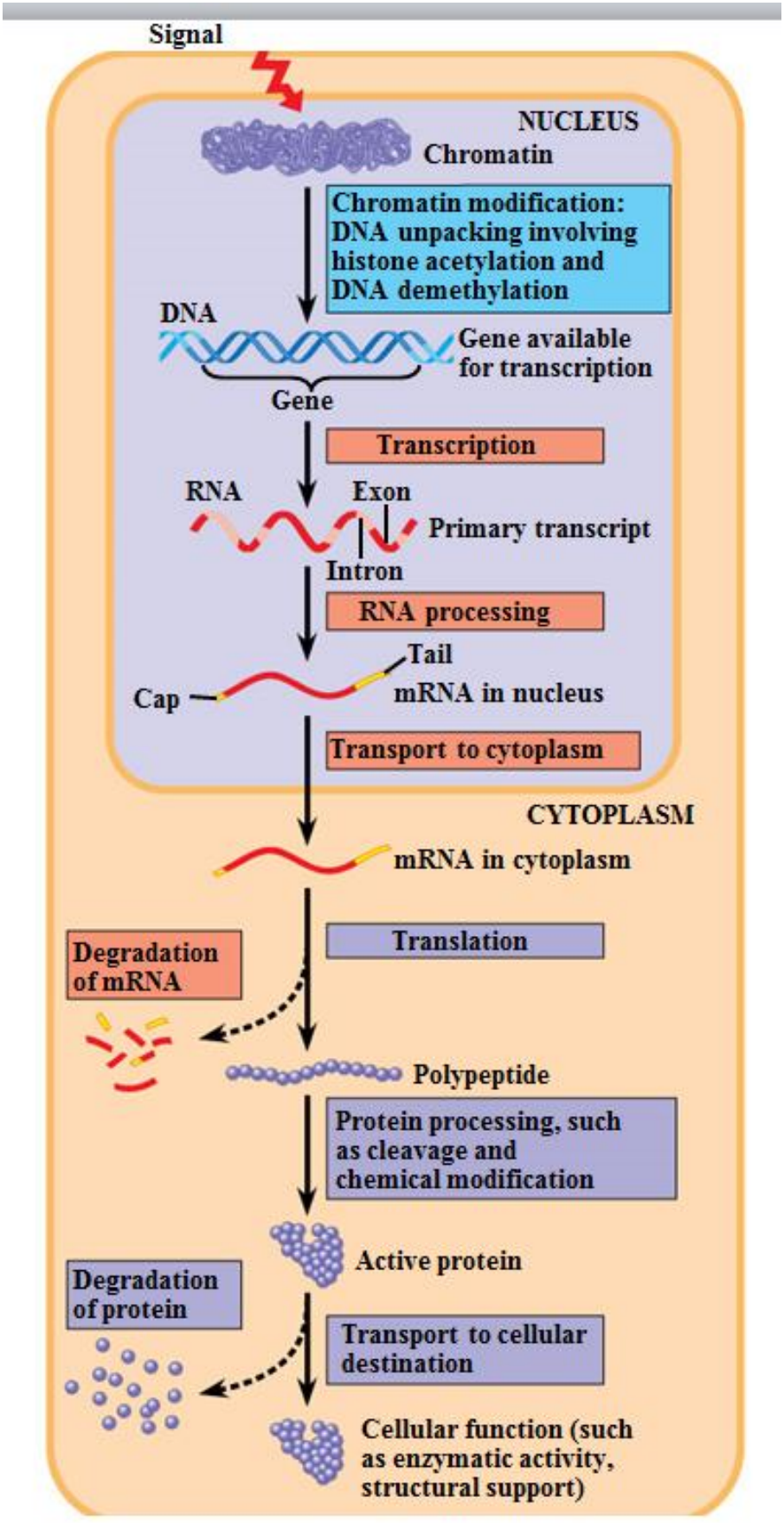
D) The *lac* operon will be expressed continuously.

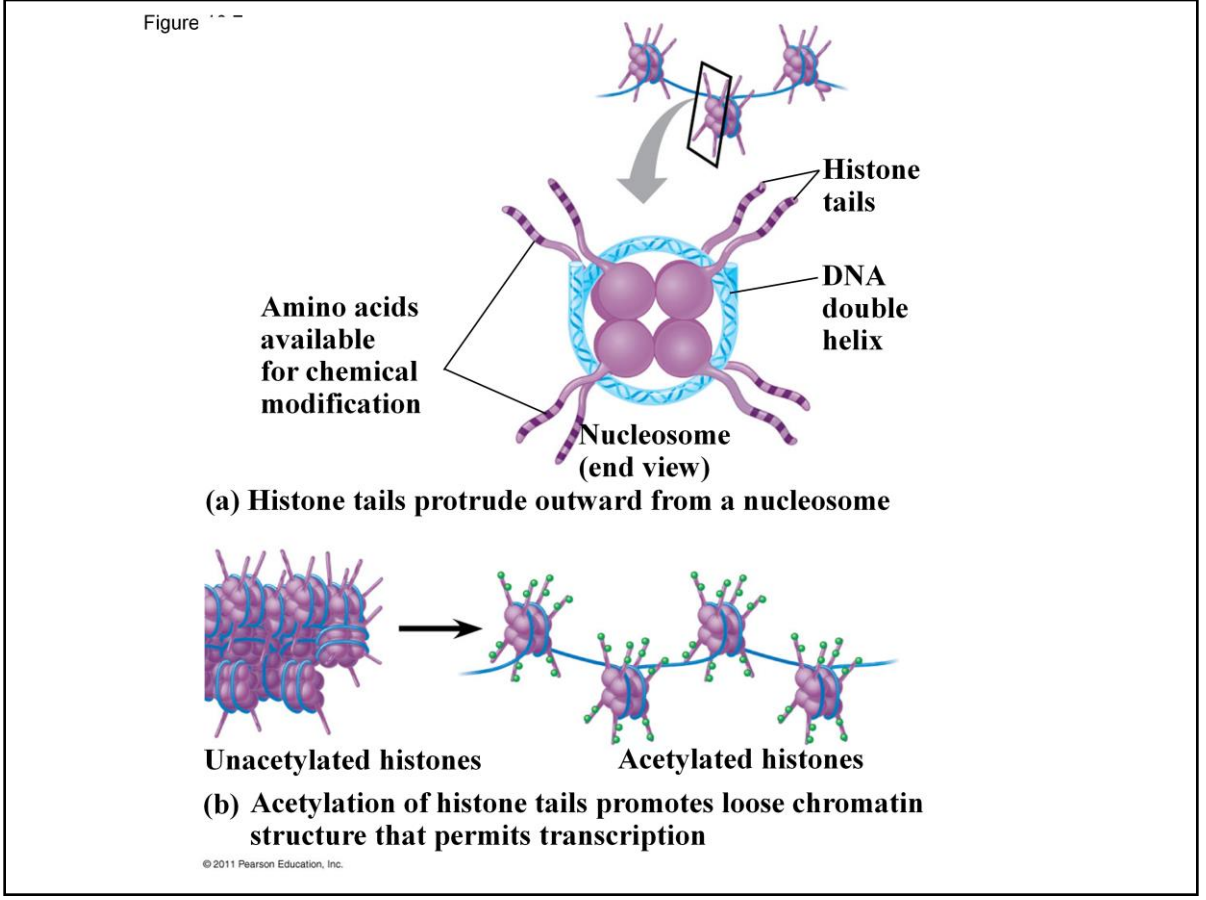
Eukaryotic gene expression is regulated at many stages

- All organisms must regulate which genes are expressed at any given time
- In multicellular organisms regulation of gene expression is essential for cell specialization

Differential Gene Expression

- Almost all the cells in an organism are genetically identical
- Differences between cell types result from **differential gene expression**, the expression of different genes by cells with the same genome
- Abnormalities in gene expression can lead to diseases including cancer
- Gene expression is regulated at many stages


Signal
NUCLEUS
Chromatin
Chromatin modification: DNA unpacking involving histone acetylation and DNA demethylation
DNA
Gene available for transcription
Gene
Transcription
RNA
Exon
Primary transcript
Intron
RNA processing
Tail
Cap
mRNA in nucleus
Transport to cytoplasm
CYTOPLASM
mRNA in cytoplasm
Translation
Degradation of mRNA
Polypeptide
Protein processing, such as cleavage and chemical modification
Active protein
Degradation of protein
Transport to cellular destination
Cellular function (such as enzymatic activity, structural support)



Histone Modifications

In **histone acetylation**, acetyl groups are attached to histones.

This **loosens chromatin structure**, thereby promoting the initiation of transcription

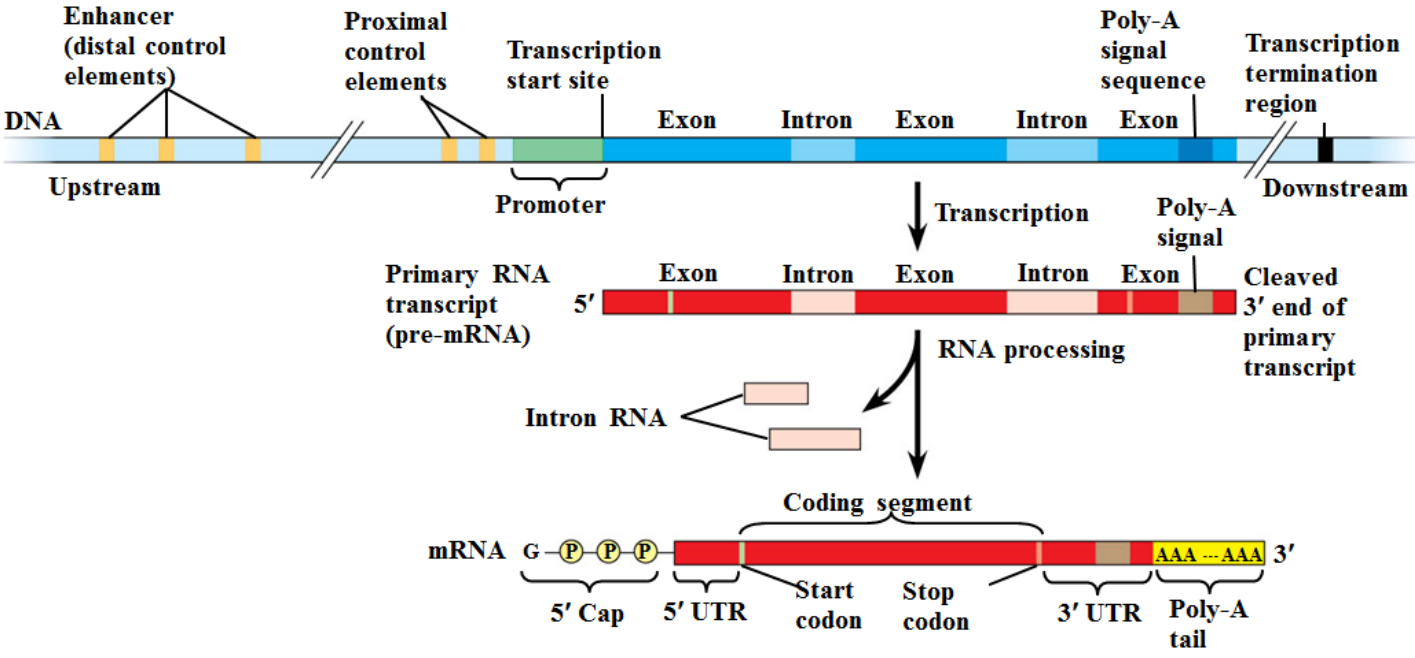
The addition of **methyl groups** (**methylation**) can **condense chromatin**

DNA methylation, the addition of methyl groups to certain bases in DNA, is associated with reduced transcription in some species

DNA methylation can cause long-term inactivation of genes in cellular differentiation

Regulation of Transcription Initiation

- Chromatin-modifying enzymes provide initial control of gene expression by making a region of DNA either more or less able to bind the transcription machinery



A eukaryotic gene and its transcript.

Associated with most eukaryotic genes are multiple **control elements**, segments of noncoding DNA that serve as binding sites for transcription factors that help regulate transcription

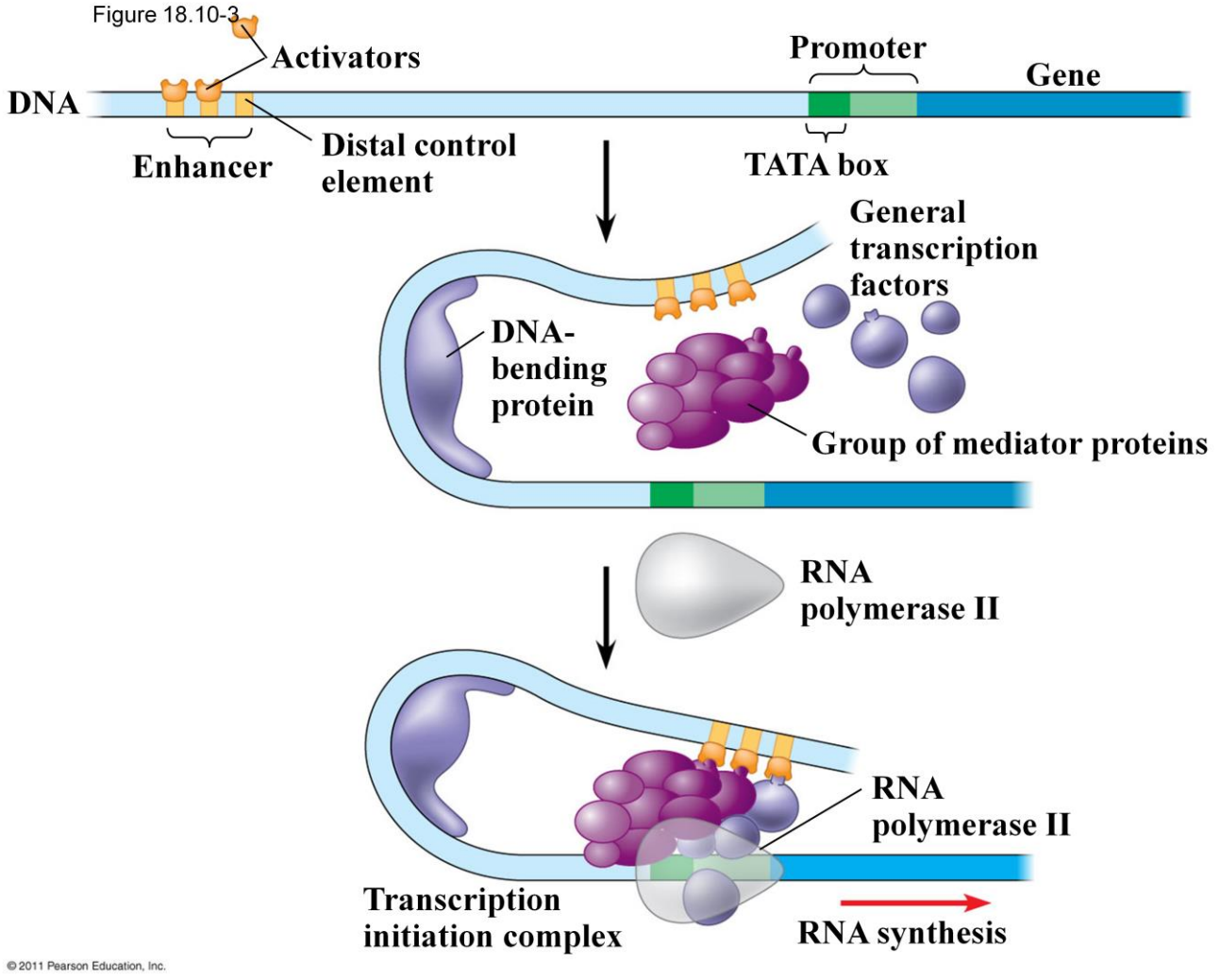
Control elements and the transcription factors they bind are critical to the precise regulation of gene expression in different cell types

The Roles of Transcription Factors

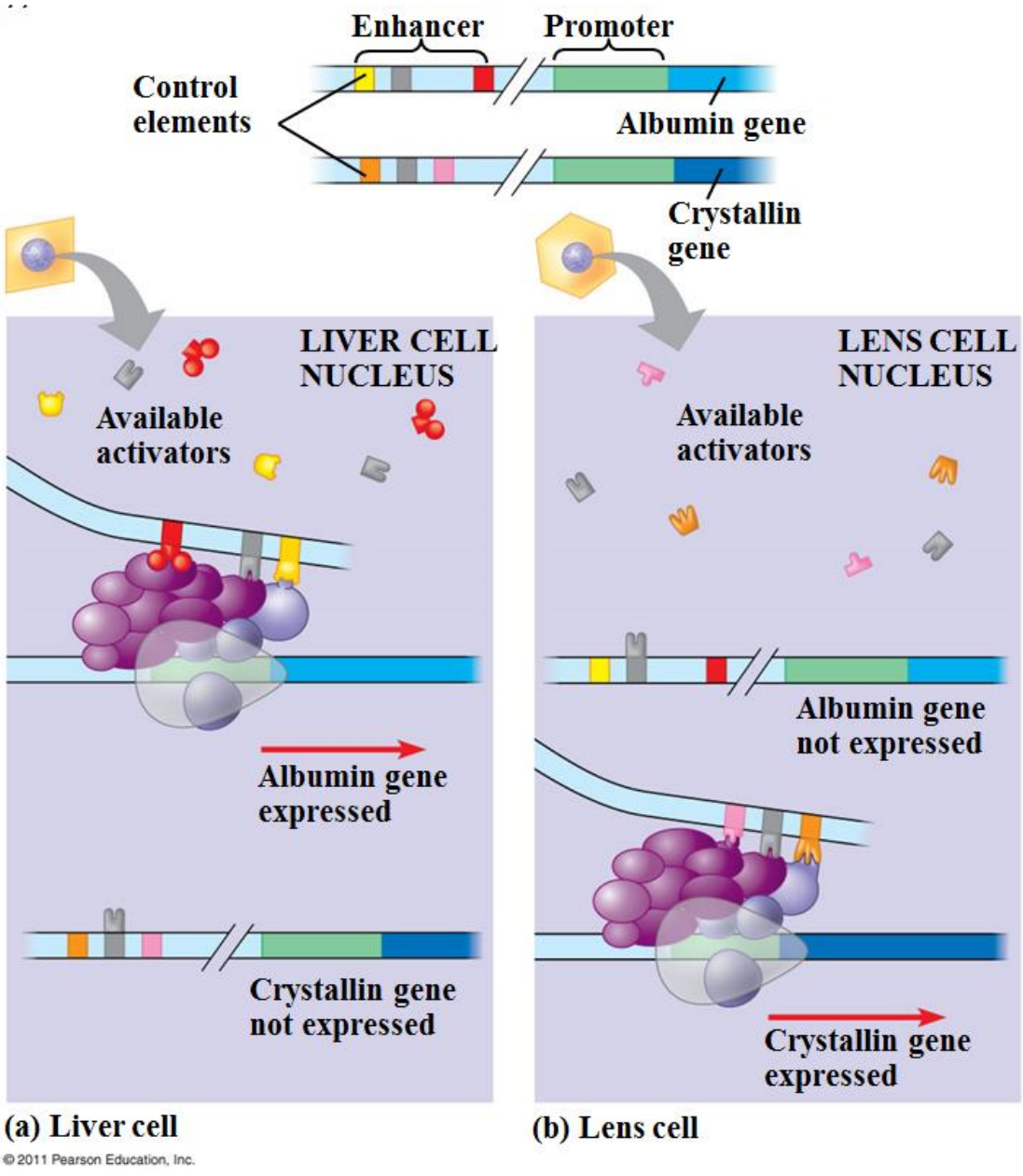
- To initiate transcription, eukaryotic RNA polymerase requires the assistance of proteins called transcription factors
- General transcription factors are essential for the transcription of all protein-coding genes
- In eukaryotes, high levels of transcription of particular genes depend on control elements interacting with specific transcription factors

Enhancers and Specific Transcription Factors

- Proximal control elements are located close to the promoter
- Distal control elements, groupings of which are called **enhancers**, may be far away from a gene or even located in an intron
- An activator is a protein that binds to an enhancer and stimulates transcription of a gene
- Activators have two domains, one that binds DNA and a second that activates transcription
- Bound activators facilitate a sequence of protein-protein interactions that result in transcription of a given gene



A model for the action of enhancers and transcription activators.

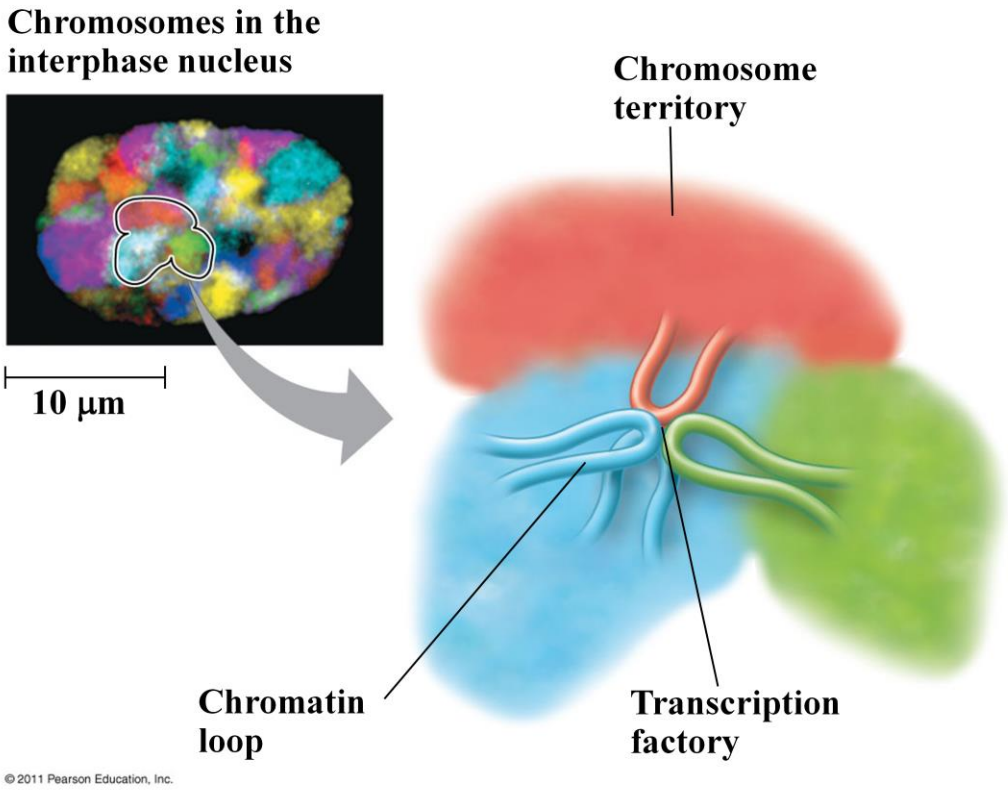


A particular combination of control elements can activate transcription only when the appropriate activator proteins are present

Coordinately Controlled Genes in Eukaryotes

- Unlike the genes of a prokaryotic operon, **each** of the co-expressed eukaryotic genes has a promoter and control elements
- These genes can be scattered over different chromosomes, but each has the same combination of control elements
- Copies of the activators recognize specific control elements and promote simultaneous transcription of the genes

Figure 18.12



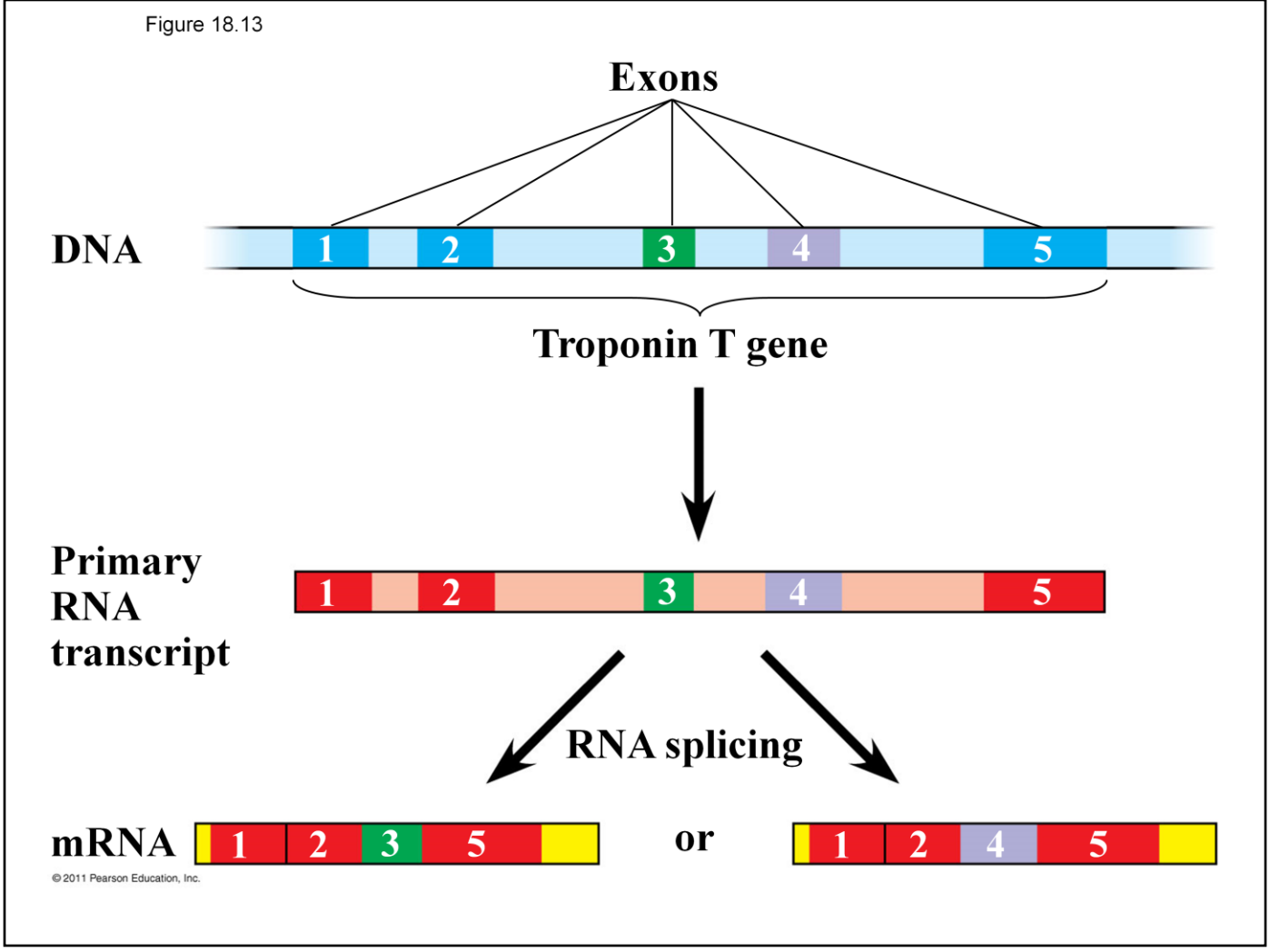
Loops of chromatin extend from individual chromosomes into specific sites in the nucleus

Loops from different chromosomes may congregate at particular sites, some of which are rich in transcription factors and RNA polymerases

These may be areas specialized for a common function

Mechanisms of Post-Transcriptional Regulation

- Regulatory mechanisms can operate at various stages after transcription
- Such mechanisms allow a cell to fine-tune gene expression rapidly in response to environmental changes



In **alternative RNA splicing**, different mRNA molecules are produced from the same primary transcript, depending on which RNA segments are treated as exons and which as introns

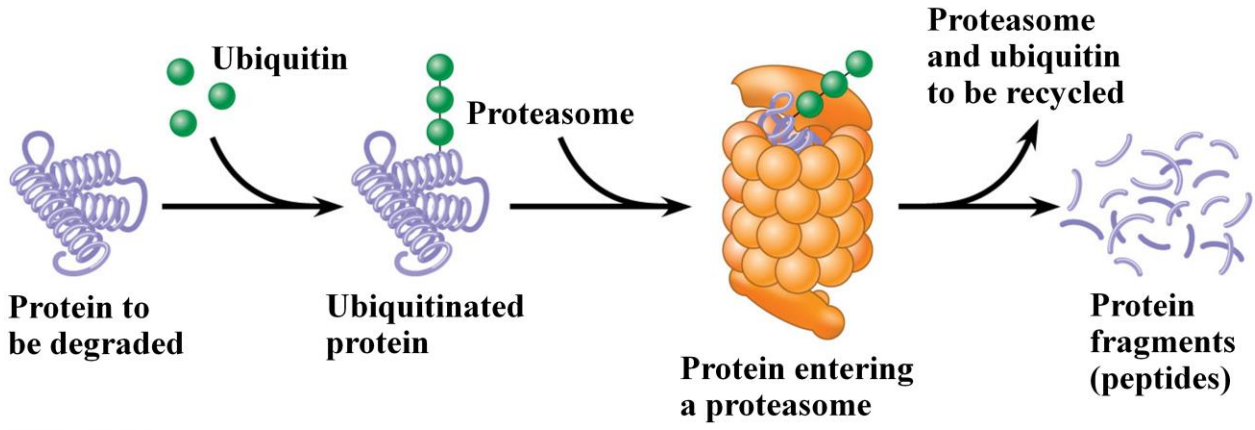
mRNA Degradation

- The life span of mRNA molecules in the cytoplasm is a key to determining protein synthesis
- Eukaryotic mRNA is more long lived than prokaryotic mRNA
- Nucleotide sequences that influence the lifespan of mRNA in eukaryotes reside in the untranslated region (UTR) at the 3′ end of the molecule

Initiation of Translation

- The initiation of translation of selected mRNAs can be regulated by proteins that bind to sequences of the mRNA
- For example, translation initiation factors are simultaneously activated in an egg following fertilization

Figure 18.14



After translation, various types of protein processing, including cleavage and the addition of chemical groups, are subject to control

Proteasomes are giant protein complexes that bind protein molecules and degrade them

Noncoding RNAs play multiple roles in controlling gene expression

- Only a small fraction of DNA codes for proteins, and a very small fraction of the non-protein-coding DNA consists of genes for RNA such as rRNA and tRNA
- A significant amount of the genome may be transcribed into noncoding RNAs (ncRNAs)
- Noncoding RNAs regulate gene expression at two points: mRNA translation and chromatin configuration

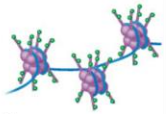
Effects on mRNAs by MicroRNAs and Small Interfering RNAs

- **MicroRNAs** (**miRNAs**) are small single-stranded RNA molecules that can bind to mRNA
- These can degrade mRNA or block its translation
- The phenomenon of inhibition of gene expression by RNA molecules is called **RNA interference (RNAi)**
- RNAi is caused by **small interfering RNAs (siRNAs)**
- siRNAs and miRNAs are similar but form from different RNA precursors

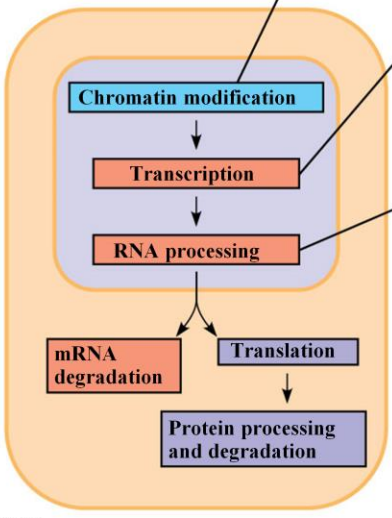
Figure 18.UN04a

Chromatin modification

- Genes in highly compacted chromatin are generally not transcribed.
- Histone acetylation seems to loosen chromatin structure, enhancing transcription.

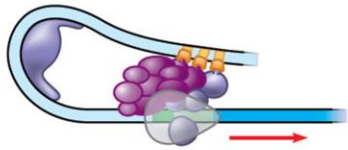


- DNA methylation generally reduces transcription.



Transcription

- Regulation of transcription initiation: DNA control elements in enhancers bind specific transcription factors.

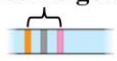


Bending of the DNA enables activators to contact proteins at the promoter, initiating transcription.

- Coordinate regulation:

Enhancer for liver-specific genes

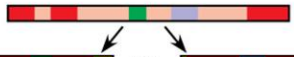
Enhancer for lens-specific genes



RNA processing

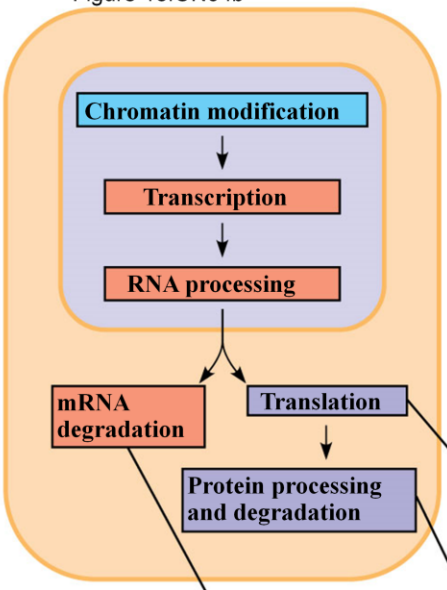
- Alternative RNA splicing:

Primary RNA transcript



mRNA

Figure 18.UN04b



Translation

- Initiation of translation can be controlled via regulation of initiation factors.

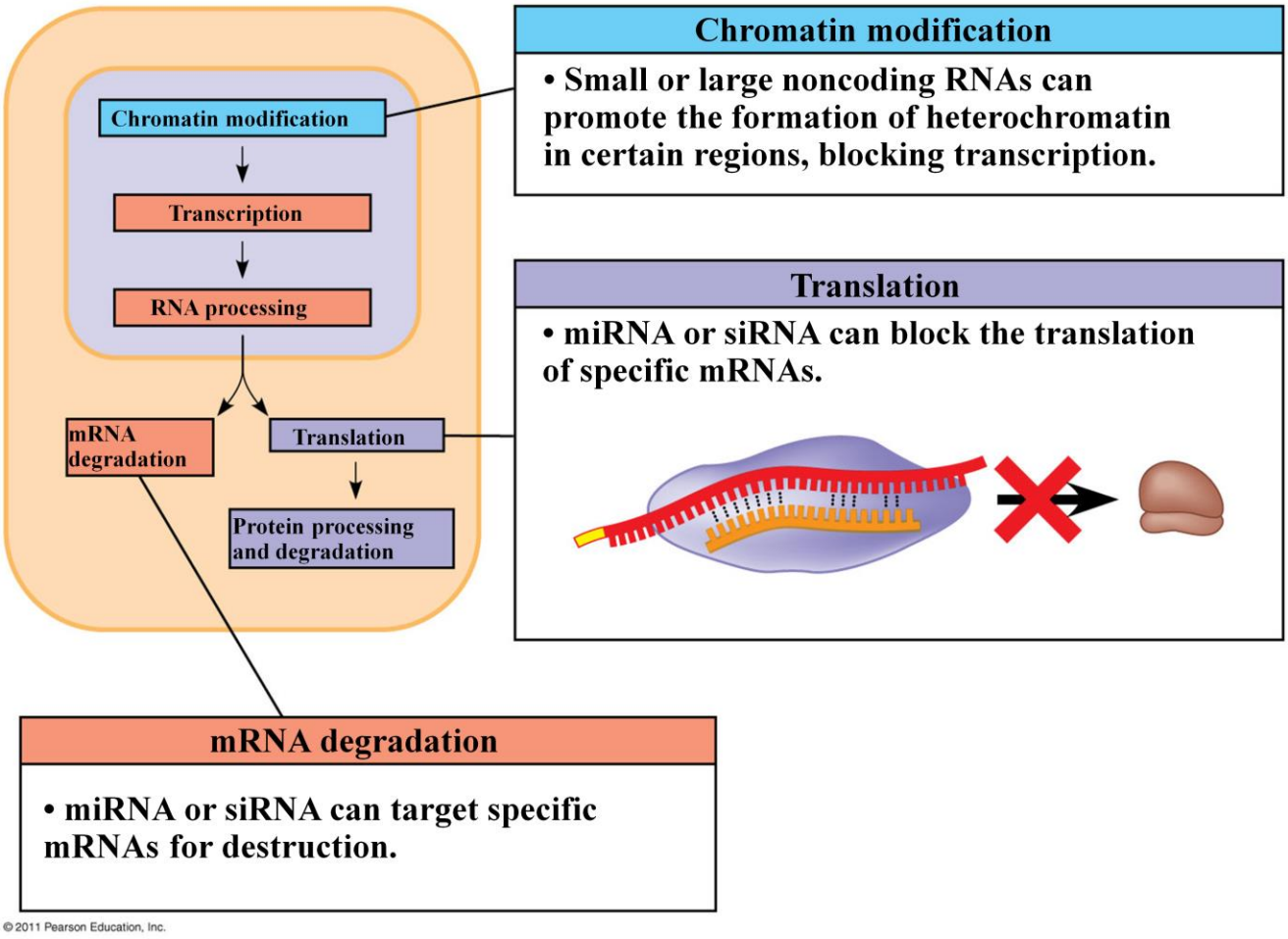
mRNA degradation

- Each mRNA has a characteristic life span, determined in part by sequences in the 5′ and 3′ UTRs.

Protein processing and degradation

- Protein processing and degradation by proteasomes are subject to regulation.

Figure 18.UN05



1. If you were to observe the activity of methylated DNA, you would expect it to

A) be replicating nearly continuously.

B) be unwinding in preparation for protein synthesis.

C) have turned off or slowed down the process of transcription.

D) be very actively transcribed and translated.

2. Two potential devices that eukaryotic cells use to regulate transcription are

A) DNA methylation and histone amplification.

B) DNA amplification and histone methylation.

C) DNA acetylation and methylation.

D) DNA methylation and histone modification.

3. Which of the following experimental procedures is most likely to hasten mRNA degradation in a eukaryotic cell?

A) enzymatic shortening of the poly-A tail

B) removal of the 5' cap

C) methylation of C nucleotides

D) methylation of histones

4. At the beginning of this century there was a general announcement regarding the sequencing of the human genome and the genomes of many other multicellular eukaryotes. There was surprise expressed by many that the number of protein-coding sequences was much smaller than they had expected. Which of the following could account for most of the rest?

A) "junk" DNA that serves no possible purpose

B) rRNA and tRNA coding sequences

C) DNA that is translated directly without being transcribed

D) non-protein-coding DNA that is transcribed into several kinds of small RNAs with biological function

5. Since Watson and Crick described DNA in 1953, which of the following might best explain why the function of small RNAs is still being explained?

A) As RNAs have evolved since that time, they have taken on new functions.

B) Watson and Crick described DNA but did not predict any function for RNA.

C) The functions of small RNAs could not be approached until the entire human genome was sequenced.

D) Changes in technology as well as our ability to determine how much of the DNA is expressed have now made this possible.

About 70% of a human's immune system comes from the symbiotic bacteria living inside our bodies. Sometimes our own immune cells unfortunately target each other or other normal tissues like the muscles and brain. A new medicine is being developed to treat one such disorder called multiple sclerosis (MS). The drug is a synthetic version of one commonly found in nature but not discovered until recently. The mechanism of action in humans is at the gene level in which several genes usually tightly regulated are faulty and always turned on. This new drug is thought to be able to suppress the genes, perhaps relieving patient symptoms.

a. Describe 2 features of gene regulation models that would allow this medication to be a success.
b. Describe 2 features of gene regulation models that could allow this medication to be a failure.

Part 2

Pathways of Information Transfer

Communication

- Requires transduction of signals from the environment, other cells or other organisms.
- Under **strong** selective pressure
  - Failure to communicate your needs for nutrients leads to death

Strategies

1. Cell-Cell direct contact
   - Plasmodesmata in Plants
2. Short Distances
- Use "local regulators" targeting nearby cells.
   - Neurotransmitters
   - Transcription Factors
   - Signal Transduction Pathways
3. Long Distances
   - **Endocrine signals (HORMONES)**
   - Nerve Action potentials

Signal Transduction Pathways

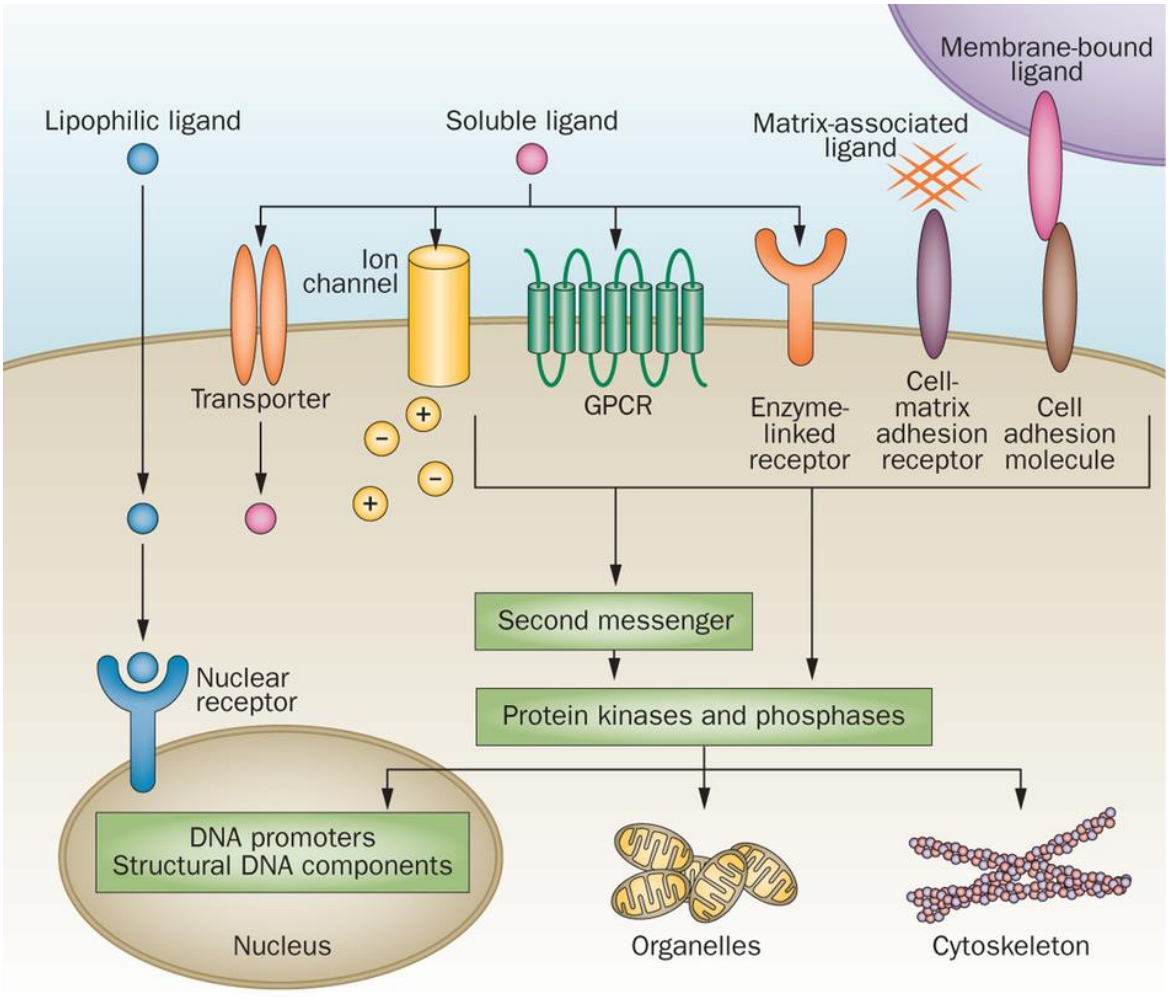
- Link signal reception with the specific response.
- Different receptors recognize different chemical messengers
  - Small chemicals (N.O., small proteins, lipids)

Steps:

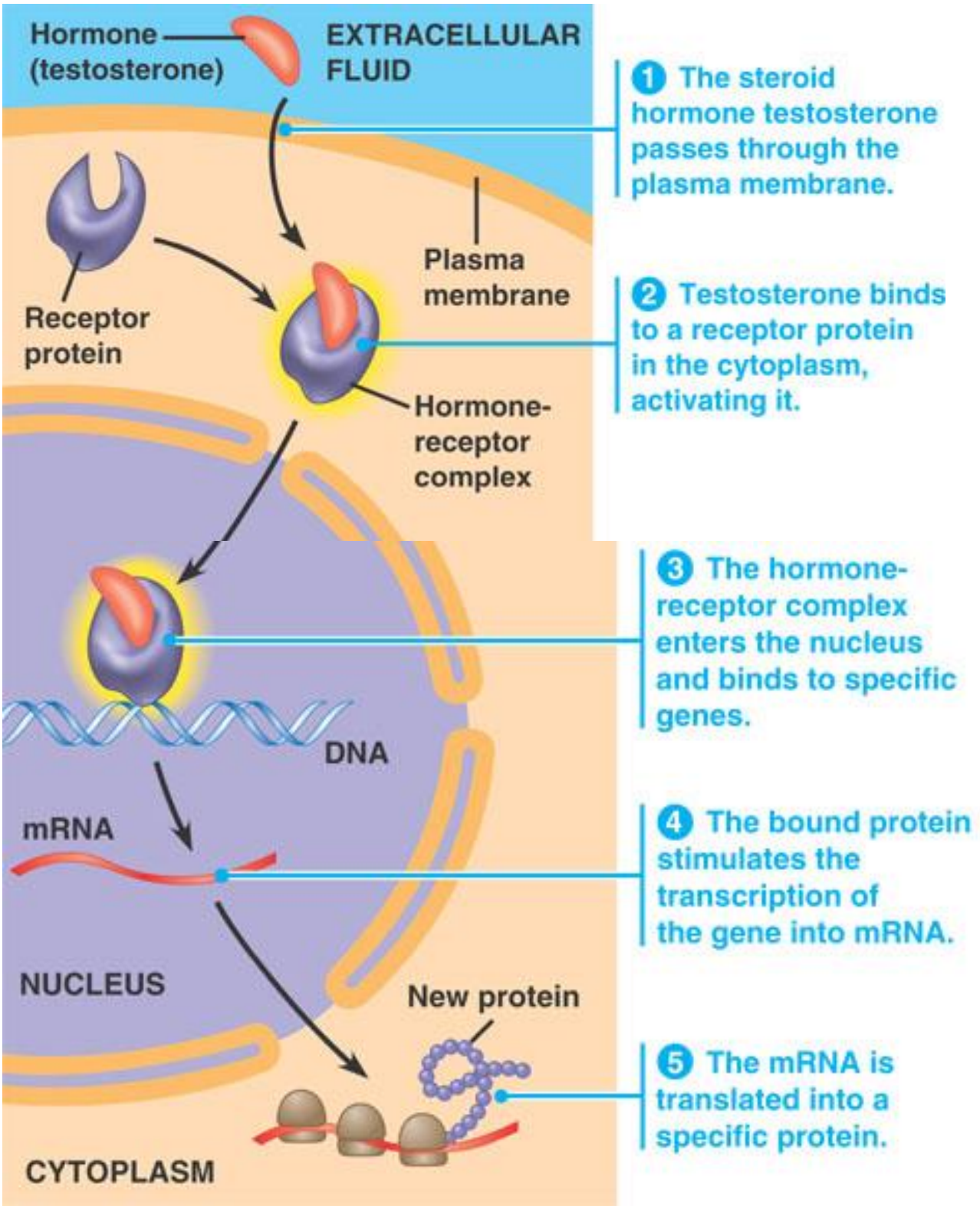
1. **Reception**: Cell receives a signal (internal or external)
2. **Transduction**: Signal is transmitted to appropriate location
3. **Response**: Signal causes a response to be generated

Signal Reception

- A signal binds to a receptor. This signal molecule is called a **ligand**.
- Receptor can be in the **cytoplasm** or on the **membrane**.

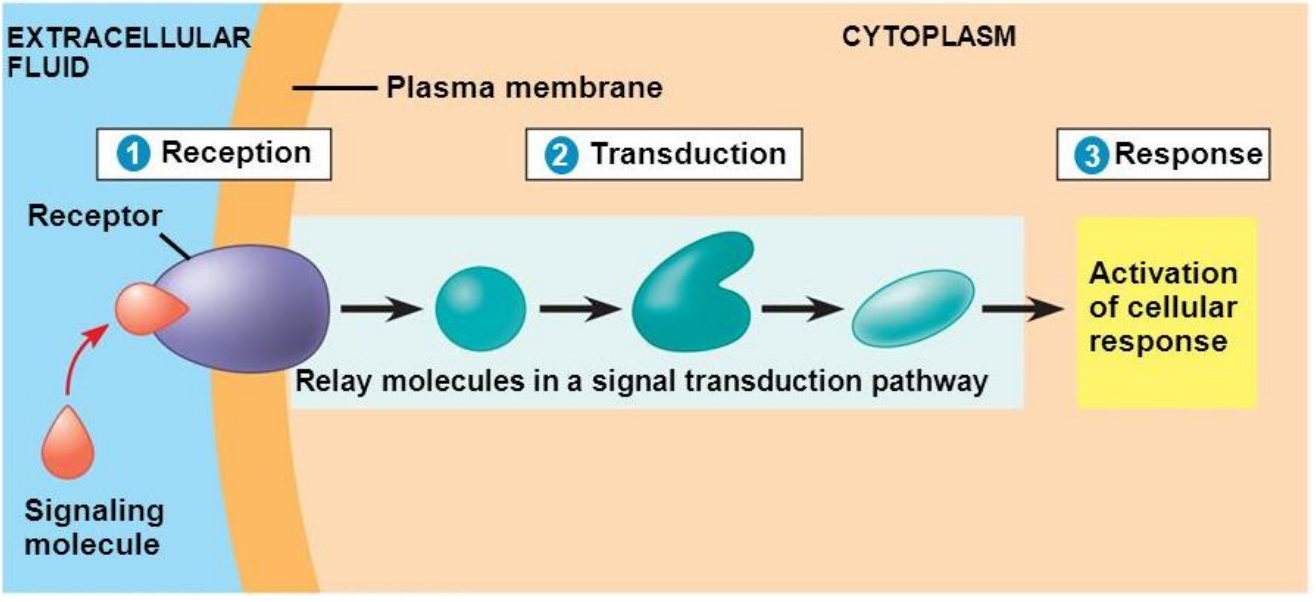


Intracellular Receptor Signaling Pathway

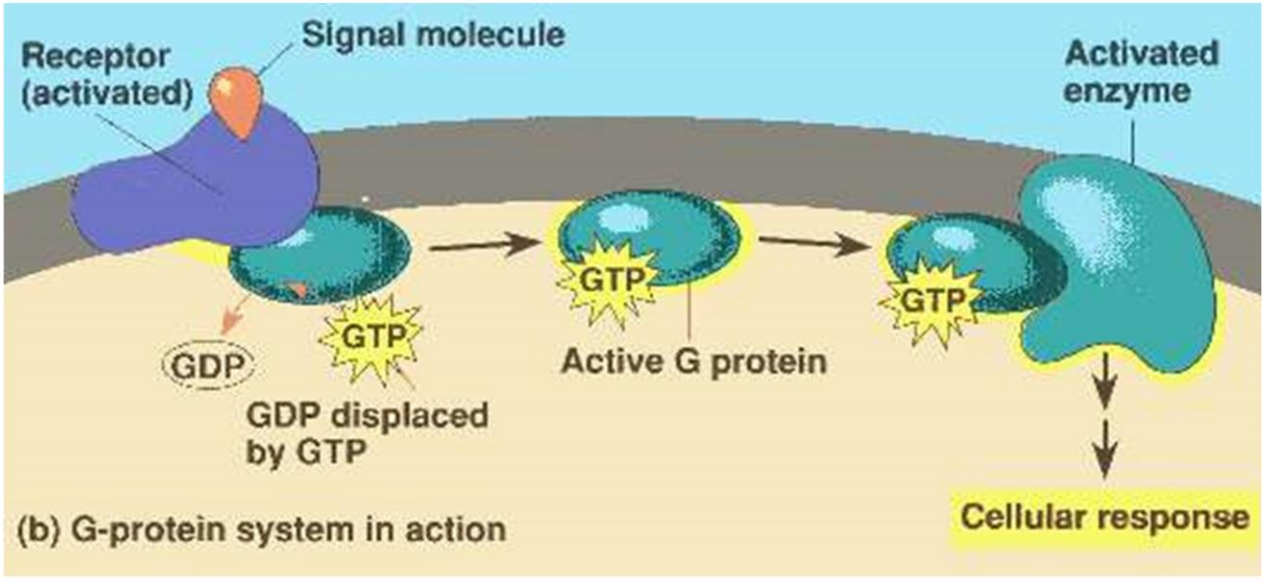


Membrane Receptors

- Ligand binds to integral protein membrane receptor
- Receptor activated/activates other molecules
- Signal is transmitted from molecule to molecule
- Final response is triggered
  - Metabolic or Nuclear

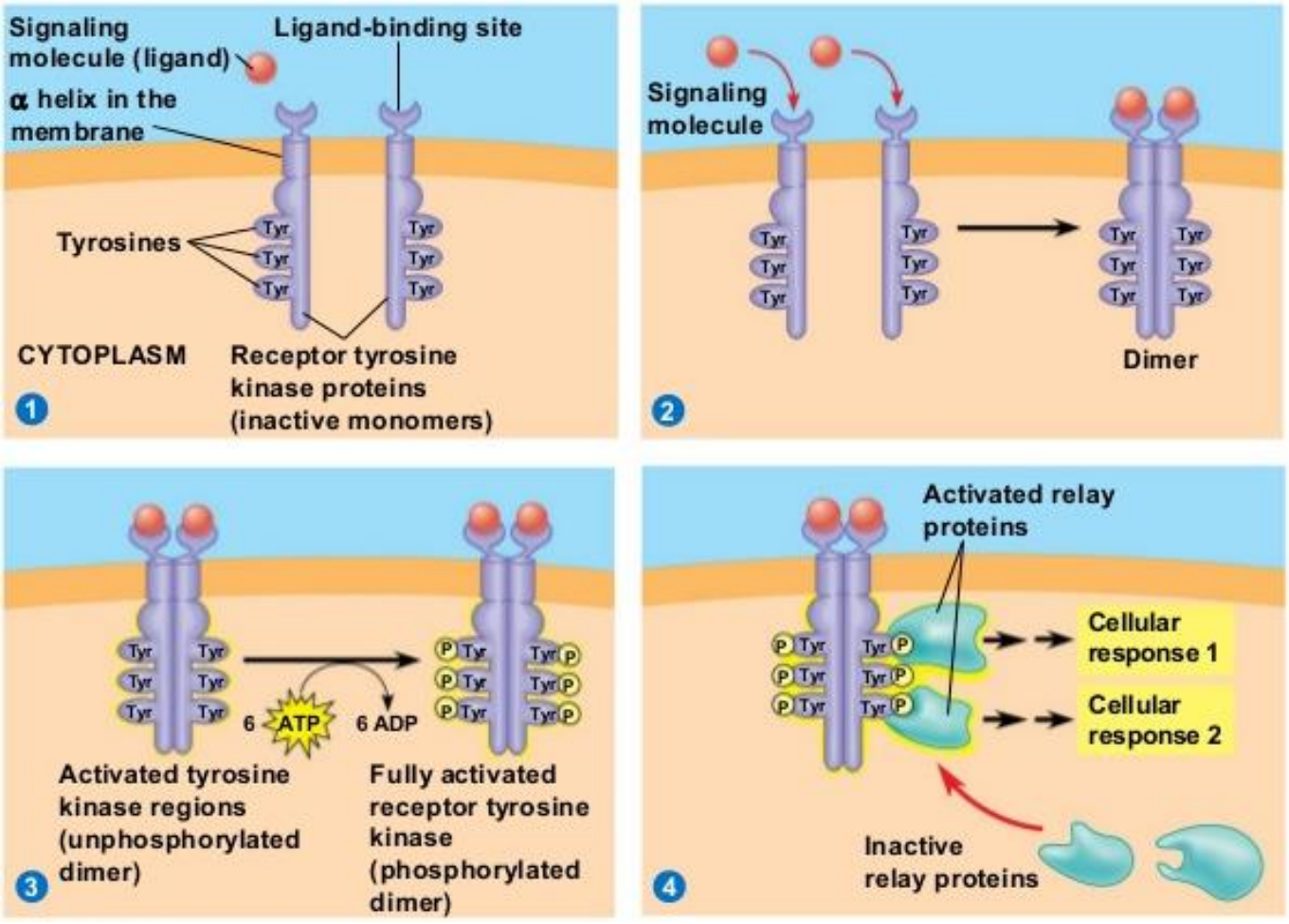


G-Protein Linked Receptors



1. Ligand **attaches** to receptor binding site.
2. Causes a G-protein to **bind** and exchange GDP for **GTP**.
3. GTP **activates** the G-protein.
4. G-protein **slides** along the membrane to reach an enzyme.
5. Enzyme is **activated**, carrying out the response.
6. Eventually, the GTP **dissociates** and the G-protein is **deactivated**.

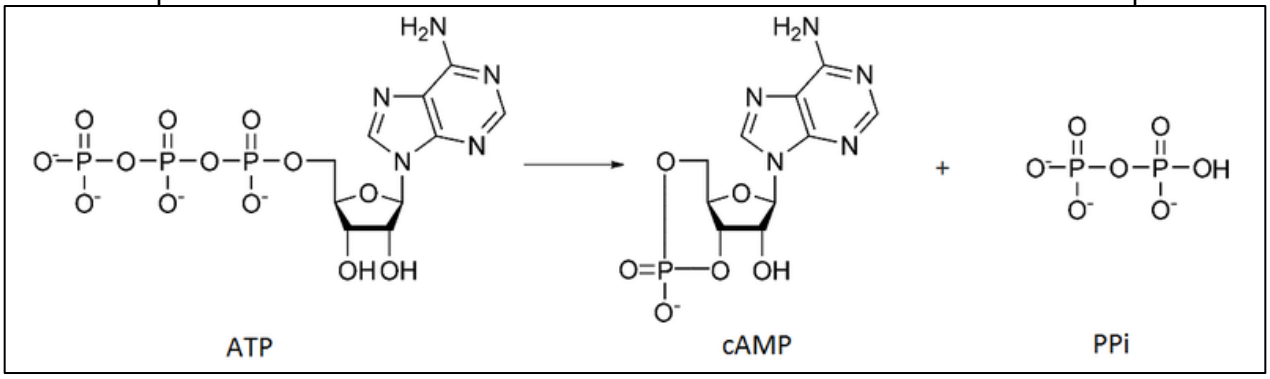
Tyrosine Kinase Receptors

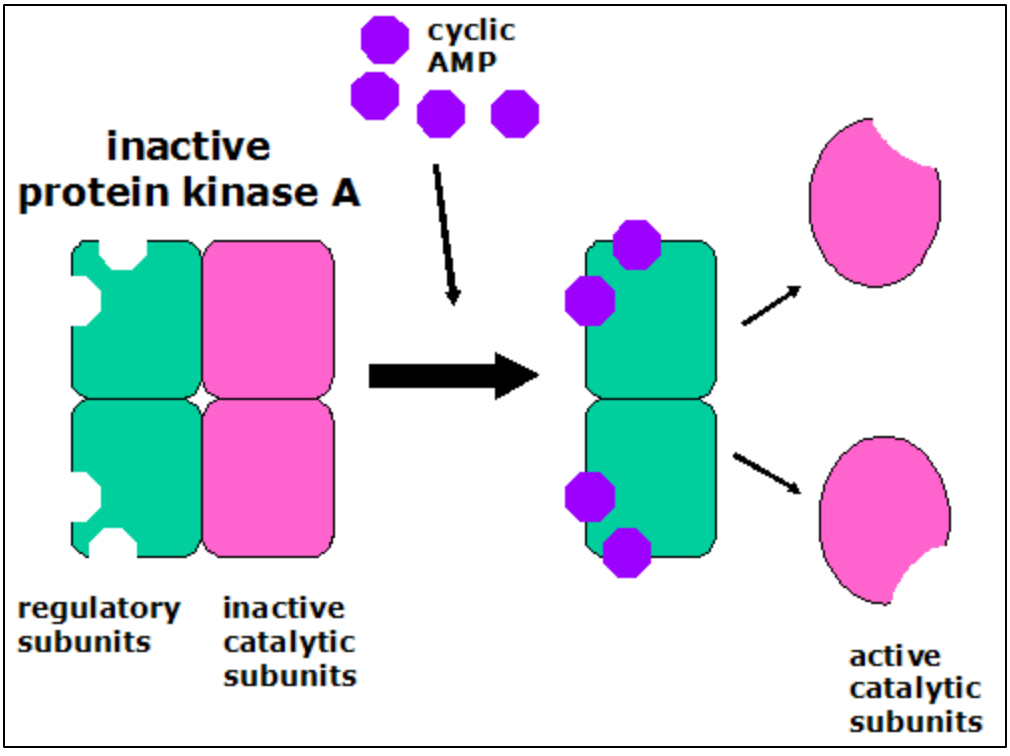


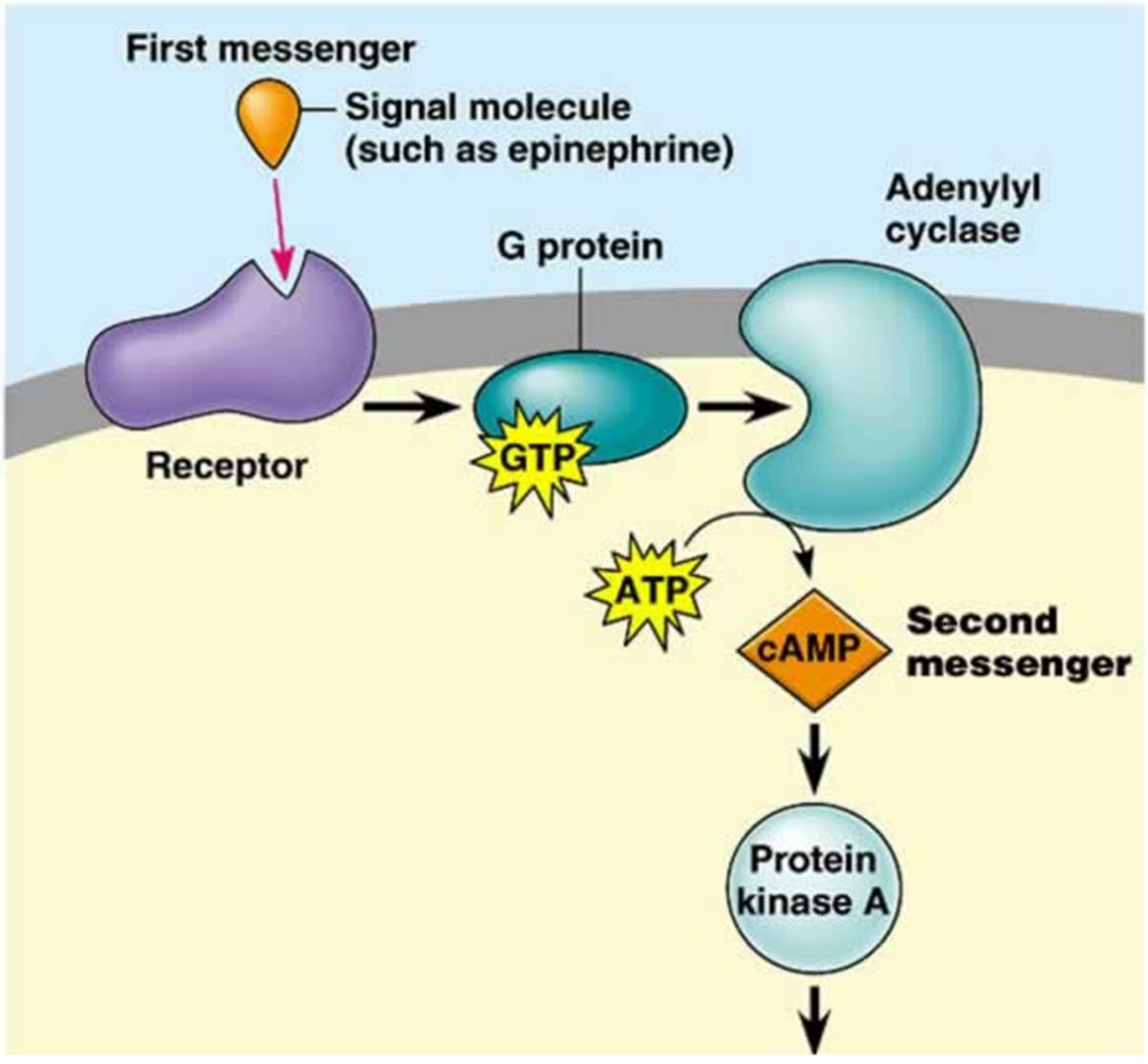
1. Ligand binds
2. Receptor dimerizes
3. ATP activates kinase region
4. Activates second messengers

Second Messenger Molecules

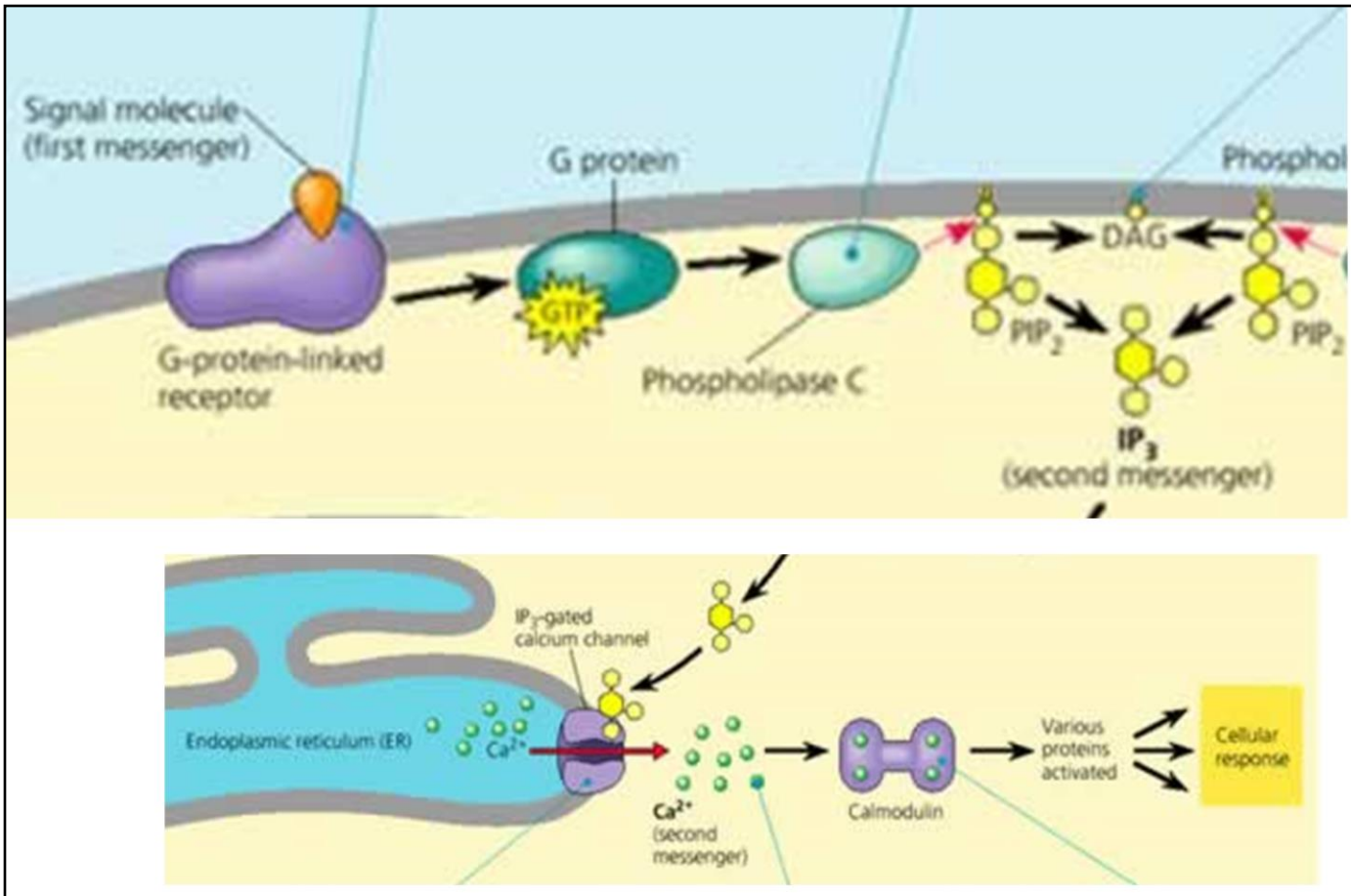
- Act as essential relay molecules
  - cAMP
  - IP_3
  - Calcium







Adenylyl cyclase enzyme converts ATP into the second messenger cAMP



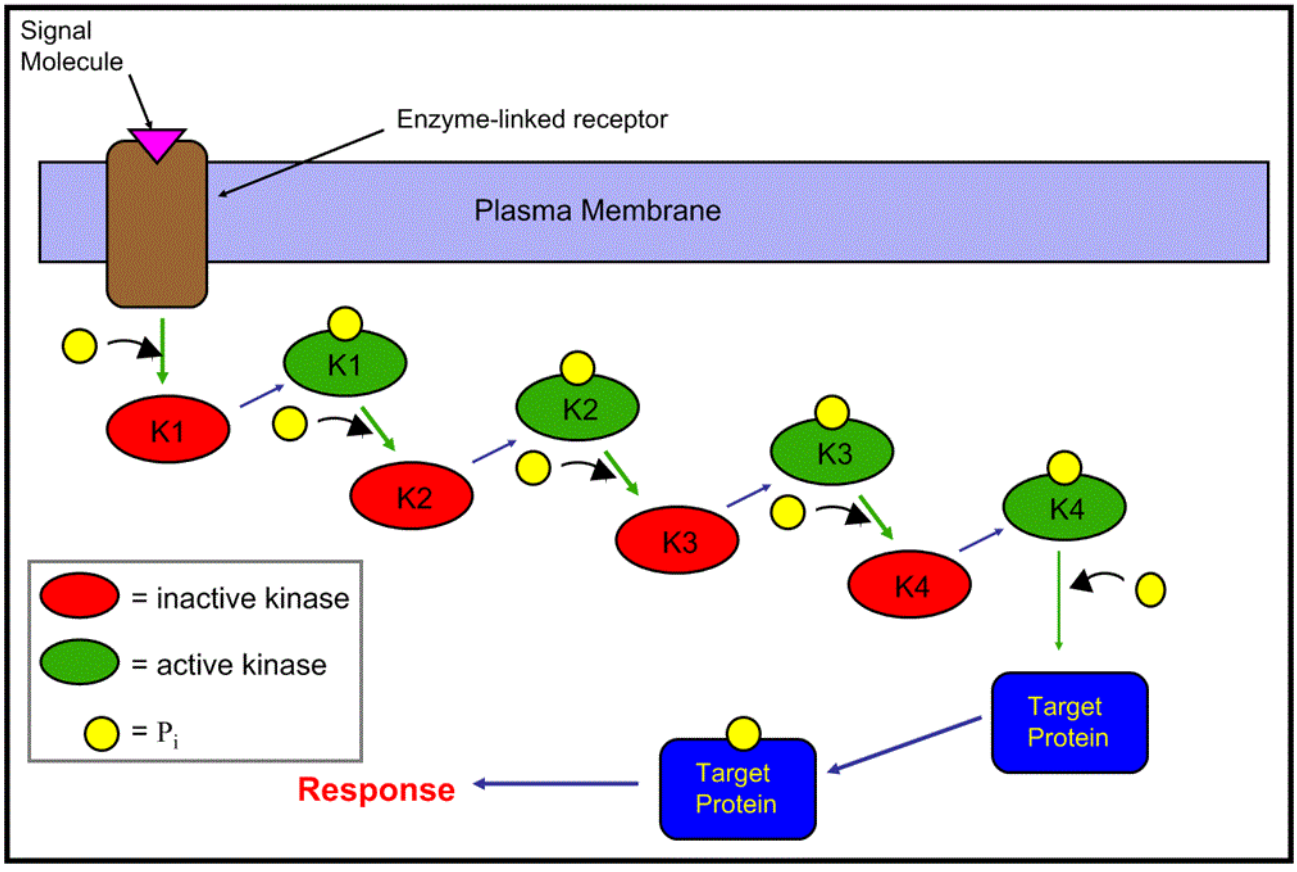
Phospholipase C converts PIP_2 into second messenger IP_3.

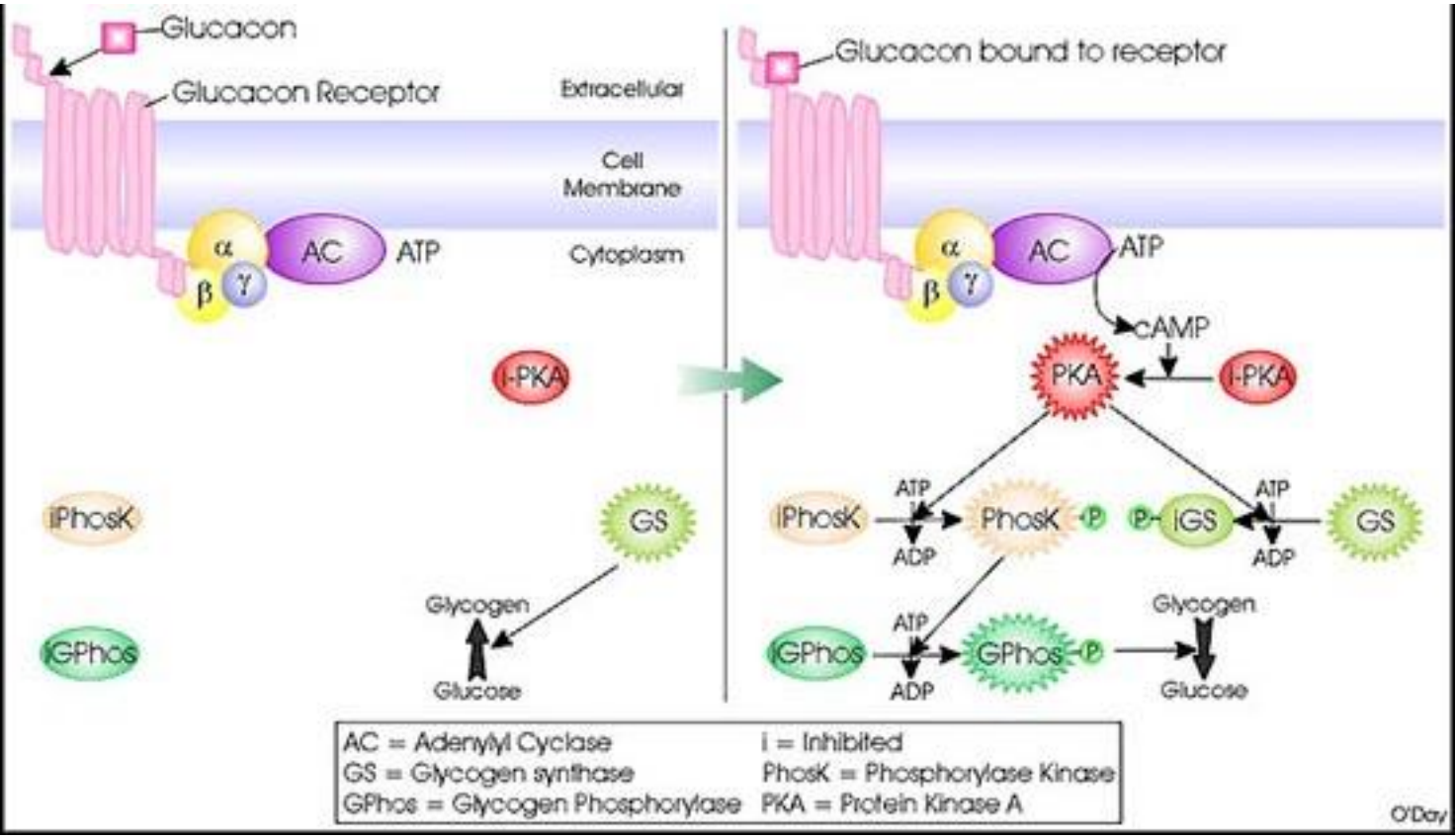
IP_3 causes calcium channels to open in ER.

Calcium binds to calmodulin, stimulating various cell responses.

Phosphorylation Cascades

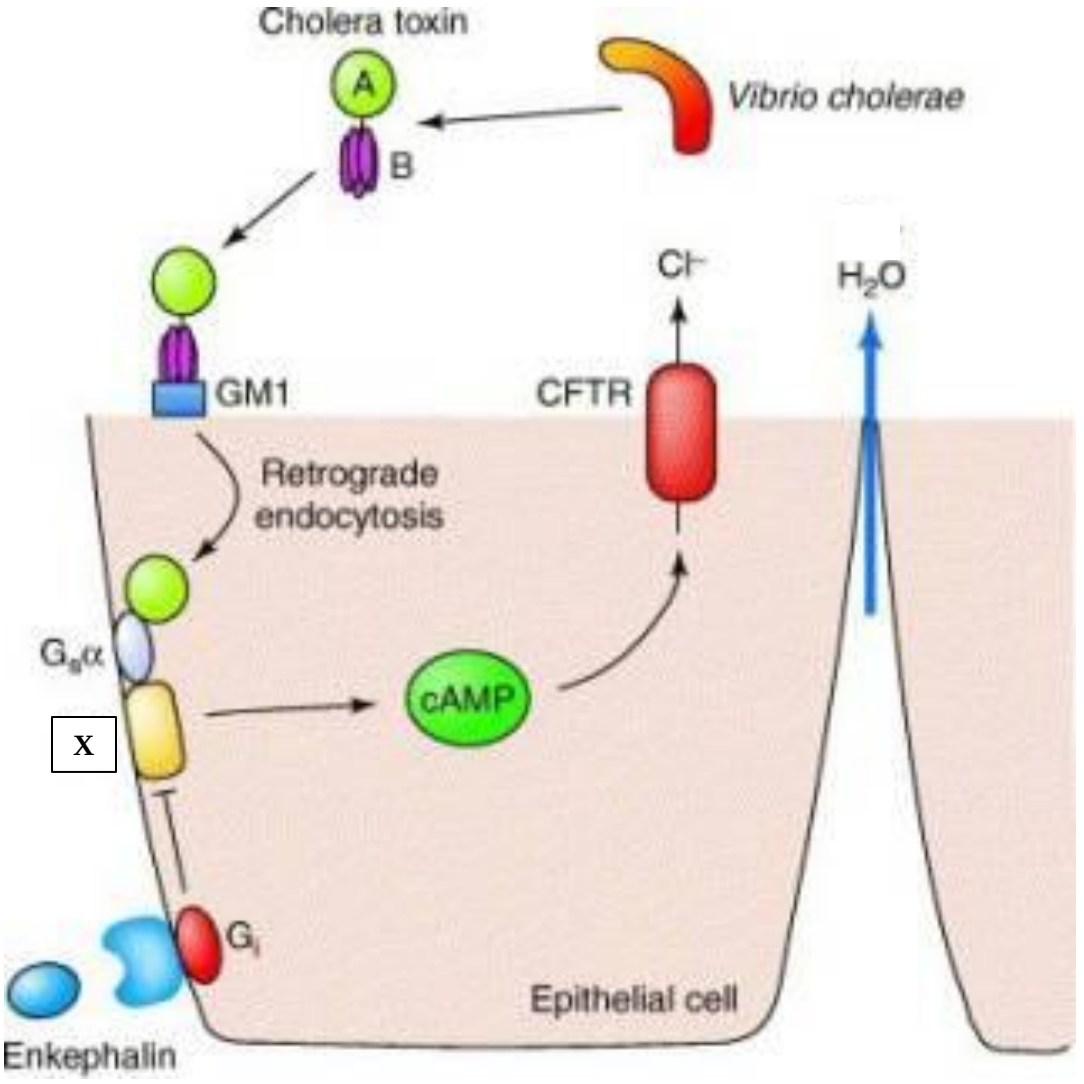
- ATP activates kinases…which activate other things.





1. Which of the following best summarizes the pathway above
    a. Intracellular receptor, lipid soluble ligand, utilizes second messengers, nuclear response.
    b. Intracellular receptor, water soluble ligand, no second messengers, metabolic response.
    c. Membrane receptor, water soluble ligand, utilizes second messengers, metabolic response.
    d. Membrane receptor, water soluble ligand, utilizes second messengers, nuclear response.

2. The gene encoding the glucagon receptor shown above undergoes a mutation. Which of the following describes a likely consequence?
    a. The receptor may no longer bind the ligand causing a decline in the metabolic pathway.
    b. The receptor will bind more ligand causing an amplification of the metabolic pathway.
    c. Glycogen synthase will remain active indefinitely.
    d. A higher level of glucose will be present in the cell.



When cholera toxin is released from the *Vibrio cholerae* bacteria in an infected intestine, it binds to epithelial cells, triggering endocytosis of the toxin. Once inside the cell, the toxin activates the G protein G_sa eventually causing a dramatic efflux of ions from infected cells, leading to watery diarrhea. One area of anti-diarrhea treatment lies in the stimulation of enkephalins, which regulate intestinal secretion by acting on other G proteins to inhibit the stimulation of cAMP synthesis induced by cholera toxin, thereby directly controlling ion transport.

3. The structure marked "**X**" is most likely
    a. ATP
    b. Phosphatase
    c. Adenylyl Cyclase
    d. Phospholipase

4. The best explanation for the diarrhea symptom of cholera toxin is
    a. cAMP is downregulated.
    b. Osmosis occurs.
    c. Too much ATP is utilized.
    d. CFTR becomes faulty.

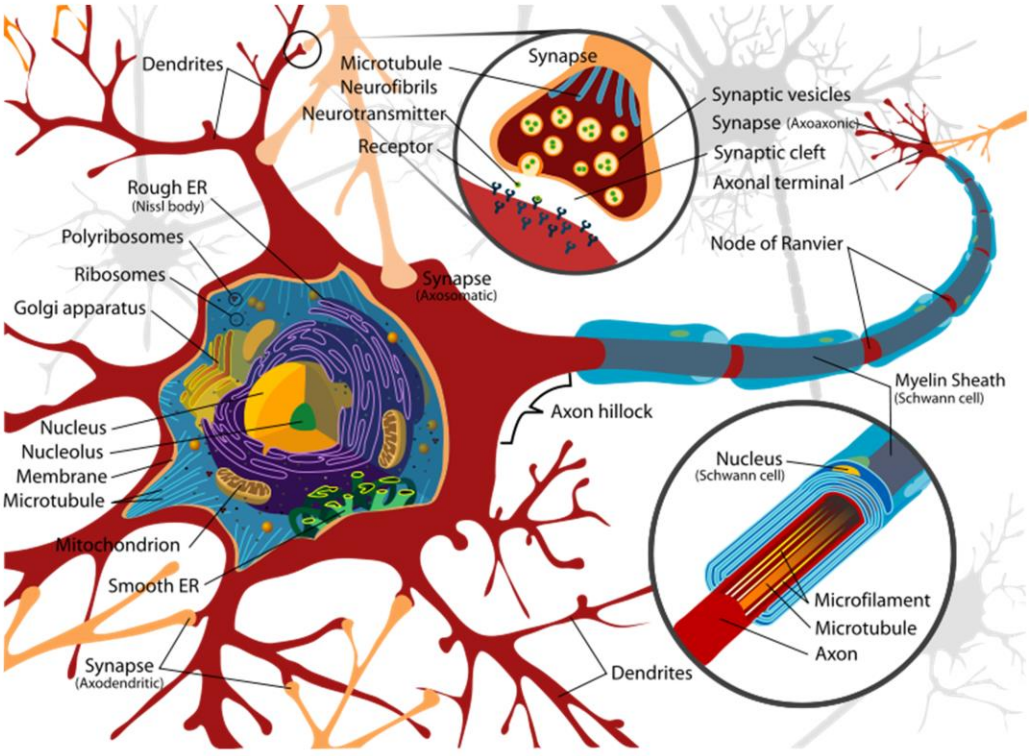
5. In accordance with the symptoms, which of the following must be true?
    a. The toxin must bind to the G protein and be quickly released.
    b. The CFTR channel must require additional factors to be regulated.
    c. The G protein must be continuously active.
    d. The toxin must also activate the G1 protein.

6. According to the diagram, which of the following may be another good candidate for therapy?
    a. A drug that targets cAMP
    b. A drug that targets the actual bacteria.
    c. A drug that targets the toxin before entering the cell.
    d. The drug discussed is the only good candidate.

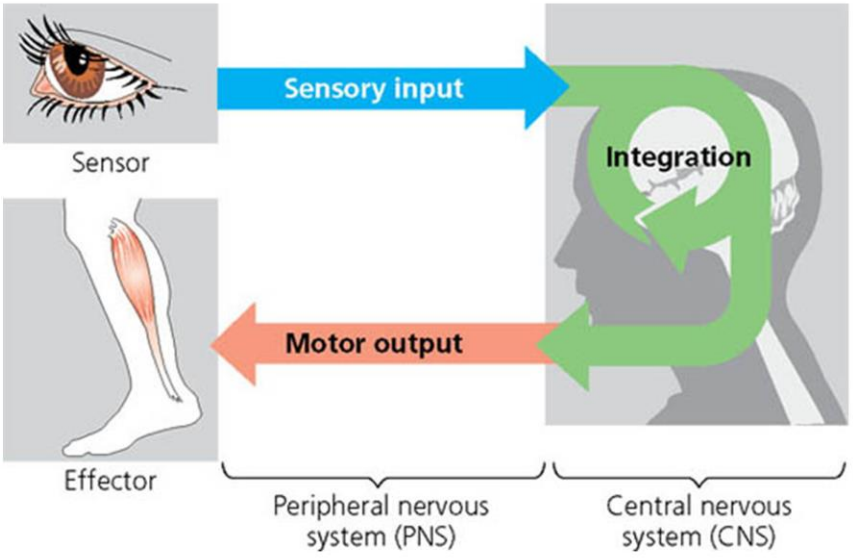
7. In a phosphorylation cascade, many similar steps are required to produce a final response. The most likely explanation for this is
    a. The amount of energy required is less than most pathways.
    b. The fewer steps in a pathway, the fewer chances for mistakes to occur.
    c. Multiple steps allow for regulation at numerous points.
    d. The same kinase is simply recycled for use in each subsequent step.

The Nervous System

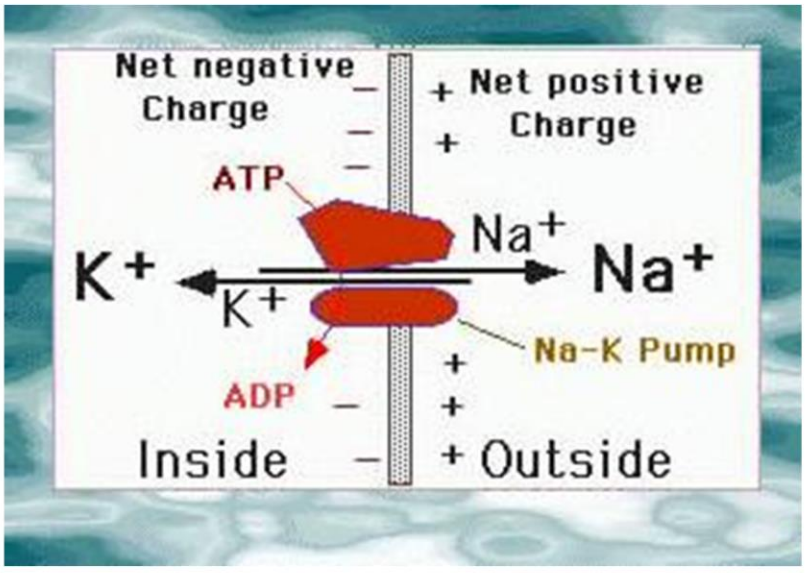
- The basic unit for signal transduction is the neuron.



Responses


Sensory input
Integration
Sensor
Motor output
Effector
Peripheral nervous system (PNS)
Central nervous system (CNS)

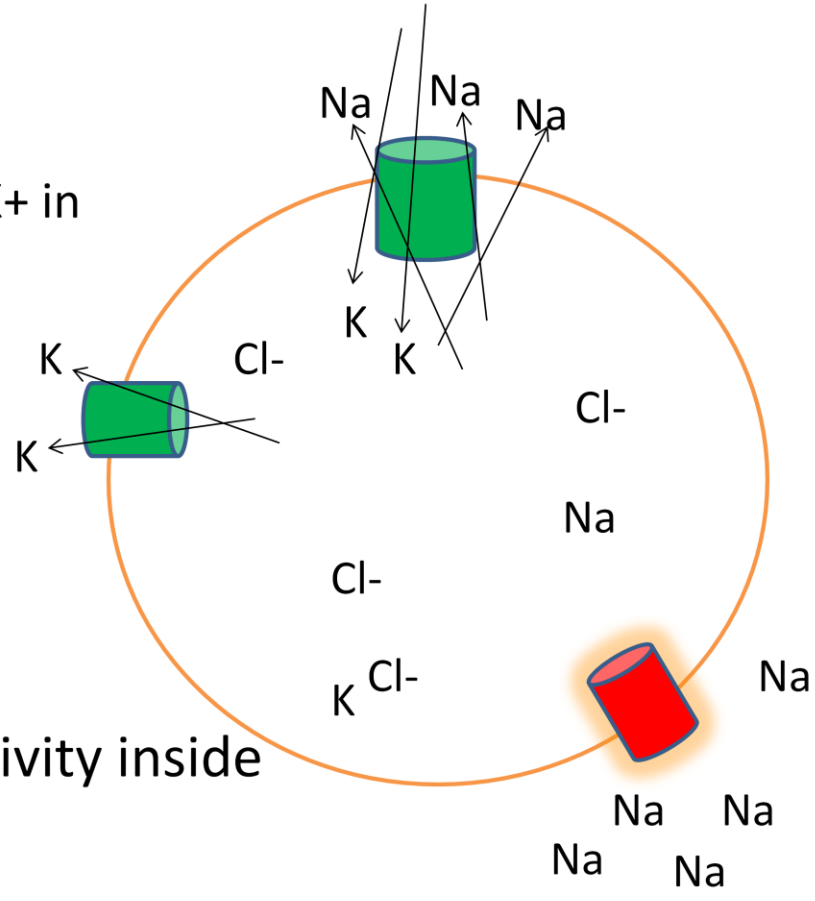
Before A Stimulus



- Cells have more negative charge inside than outside
- Resting membrane potential -70mV
- No signaling
- Powered by ATP

Before A Stimulus

- Na+/K+ Pump
  - 3 Na+ OUT for 2 K+ in
    - Less + inside
    - More - inside
- Na Channels
  - CLOSED
    - No + Influx
- K Channels
  - Some open
    - Slight + Eflux
- Cl increases negativity inside

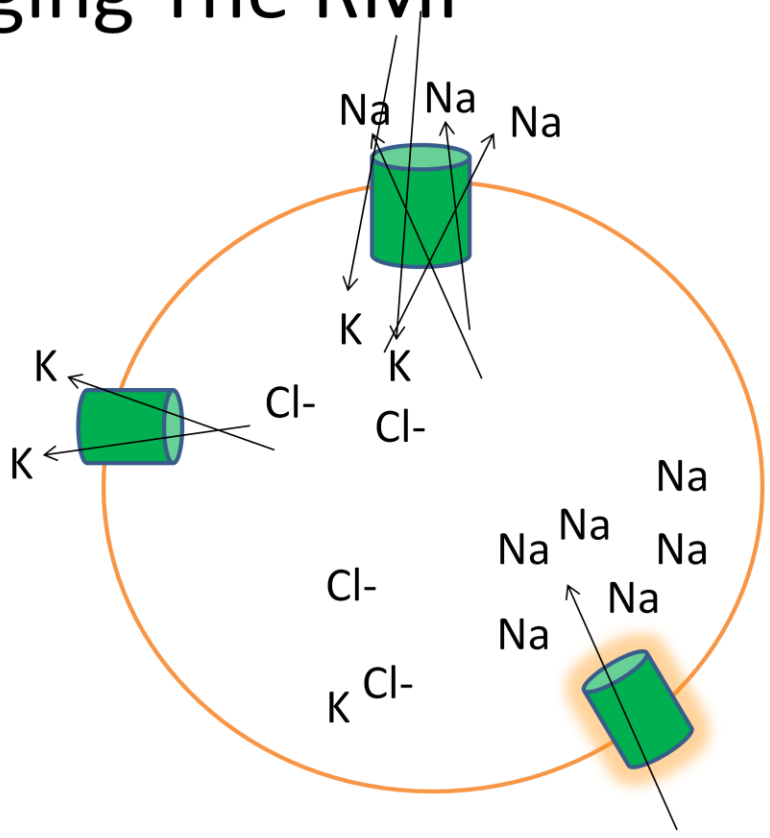


Stimulus Sensed

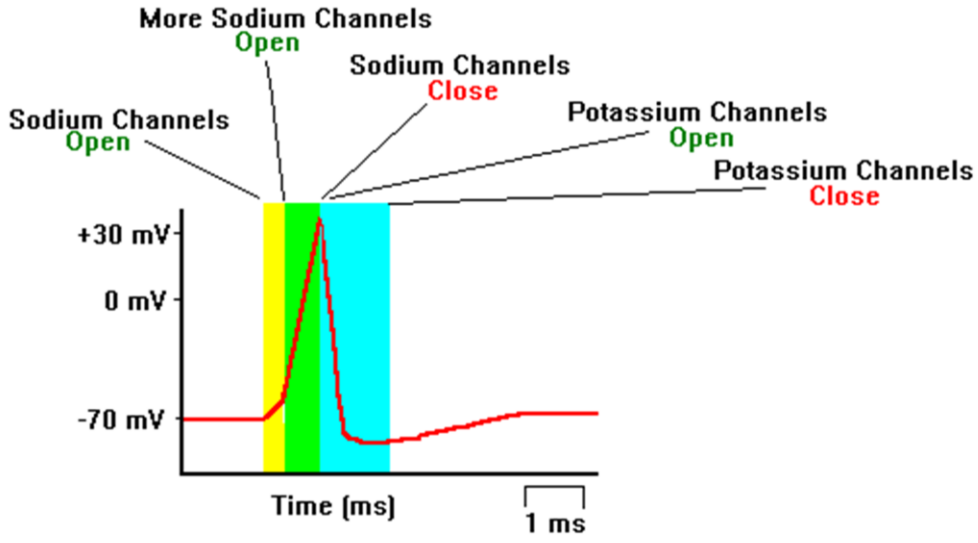
- Sensory Transduction
  - Initiates a change in RMP
    - Hunger
    - Pain
    - Light
    - Temperature
    - Chemicals
  - Change in the RMP = Receptor Potential
  - Open ion channels & depolarize membrane

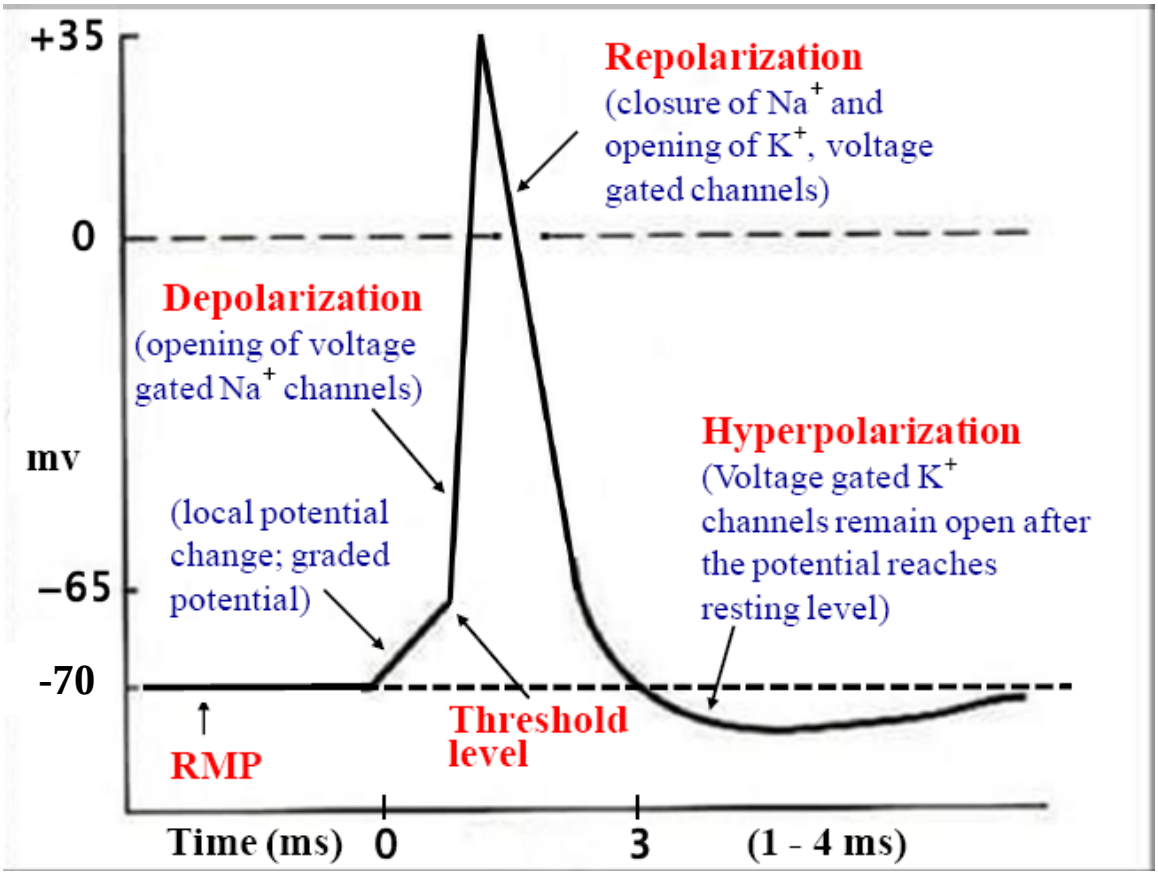
Changing The RMP

- Na Channels
  - OPEN
- Causes RAPID influx of Na
- Makes inside suddenly more POSITIVE
- Depolarization



Action Potential

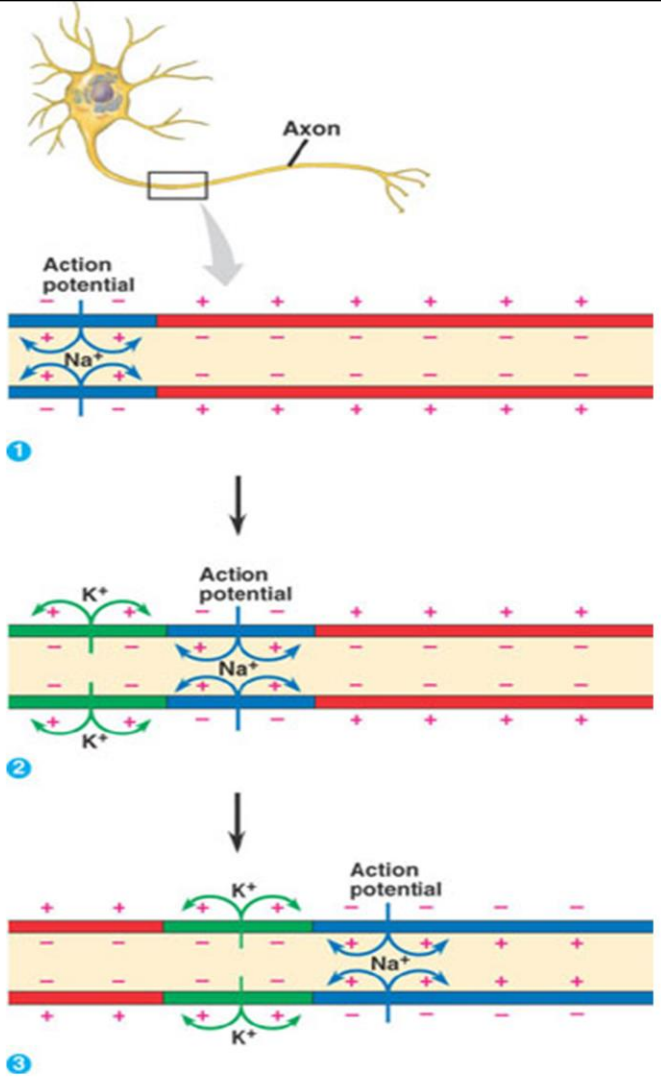




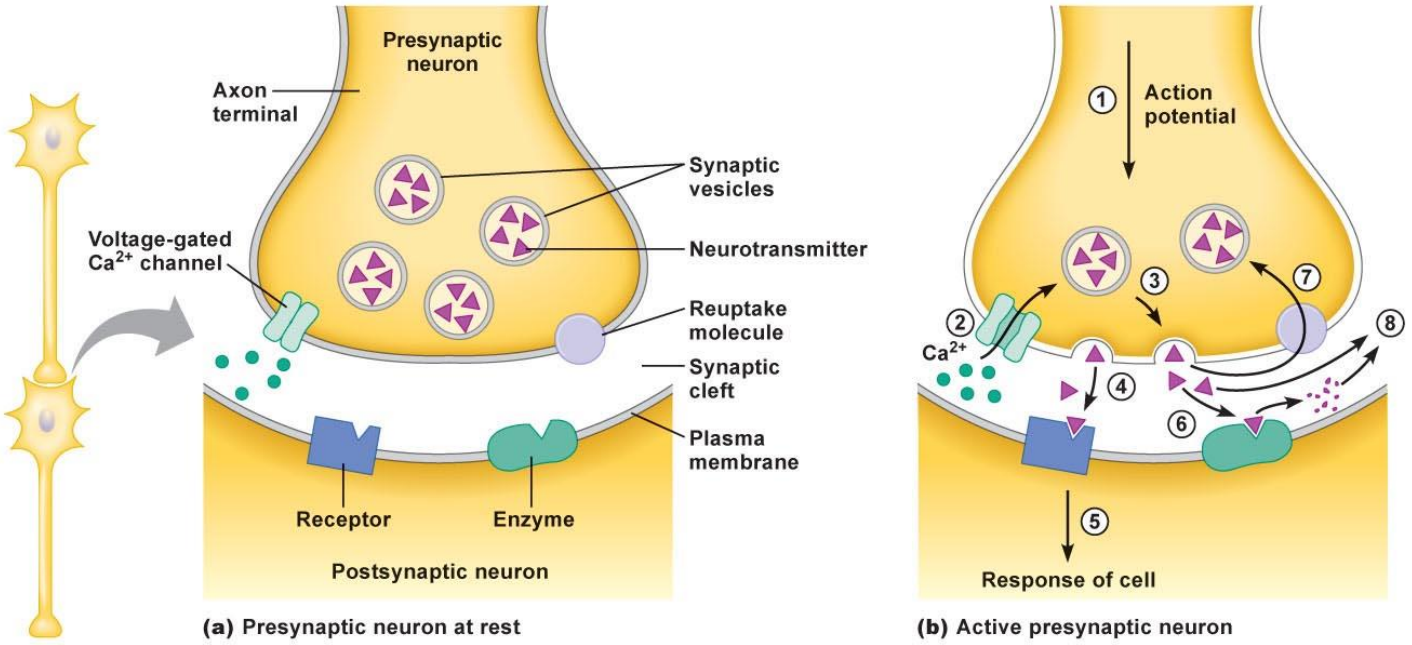
Transmission

- Strength of 1st depolarization causes continuous depolarizations along the nerve

- Propogation



Continuing the Signal



1. Action potential arrives at presynaptic membrane.

2. Calcium channels open, moving calcium into the presynaptic neuron.

3. Calcium binds to vesicles, causing their release into synaptic cleft.

4. Neurotransmitters trigger action potential in postsynaptic cell.

   Acetylcholine Epinephrine Dopamine

   Seratonin GABA

1) The operation of the sodium-potassium "pump" moves

A) sodium and potassium ions into the cell.

B) sodium and potassium ions out of the cell.

C) sodium ions into the cell and potassium ions out of the cell.

D) sodium ions out of the cell and potassium ions into the cell.

2) The surface on a neuron that discharges the contents of synaptic vesicles is the

A) presynaptic membrane.

B) postsynaptic membrane

C) dendrite

D) axon hillock

3) Neurotransmitters are released from axon terminals via

A) osmosis.

B) exocytosis.

C) diffusion.

D) transcytosis.

4) The following steps refer to various stages in transmission at a chemical synapse.

1. Neurotransmitter binds with receptors associated with the postsynaptic membrane.
2. Calcium ions rush into neuron's cytoplasm.
3. An action potential depolarizes the membrane of the axon terminal.
4. The ligand-gated ion channels open.
5. The synaptic vesicles release neurotransmitter into the synaptic cleft.

Which sequence of events is correct?

A) 1 → 2 → 3 → 4 → 5

B) 2 → 3 → 5 → 4 → 1

C) 3 → 2 → 5 → 1 → 4

D) 4 → 3 → 1 → 2 → 5

5) For a neuron with an initial membrane potential at -70 mV, an increase in the movement of potassium ions out of that neuron's cytoplasm would result in

A) the depolarization of the neuron.

B) the hyperpolarization of the neuron.

C) the replacement of potassium ions with sodium ions.

D) the replacement of potassium ions with calcium ions.

6) Two fundamental concepts about the ion channels of a "resting" neuron are that the channels

A) are always open, but the concentration gradients of ions frequently change.

B) are always closed, but ions move closer to the channels during excitation.

C) open and close depending on stimuli, and are specific as to which ion can traverse them.

D) open and close depending on chemical messengers, and are nonspecific as to which ion can traverse

7) After the depolarization phase of an action potential, the resting potential is restored by

A) the opening of sodium activation gates.

B) the opening of voltage-gated potassium channels and the closing of sodium channels.

C) a decrease in the membrane's permeability to potassium and chloride ions.

D) a brief inhibition of the sodium-potassium pump.

8) Assume that excessive consumption of ethanol increases the influx of negative chloride ions into "common sense" neurons whose action potentials are needed for you to act appropriately and not harm yourself or others. Thus, any resulting poor decisions associated with ethanol ingestion are likely due to

A) increased membrane depolarization of "common sense" neurons.

B) decreased membrane depolarization of "common sense" neurons.

C) more action potentials in your "common sense" neurons.

D) no action potentials in your "common sense" neurons.